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A TOXIC FACTOR IN EXPERIMENTAL TRAUMATIC SHOCK*

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MEDICAL investigations are often the product of a number of workers. This is particularly true in these years of war emergency, when groups of men co-operate in an attempt to solve problems quickly. Thus, in our search for a toxic factor in the shock syndrome, credit for the results is largely due to my associates, who have contributed much of the work and many of the ideas. Those who have worked throughout have been Drs. Austin Brues, Ira Nathanson, Alfred Pope and Paul Zamecnik and Miss Abby Nutt; others have collaborated in part of the work, namely, Drs. Waldo Cohn, René Dubos, Cynthia Pierce and Seymour Kety and Miss Dorothy Tibbetts. It is in their name that I make this summarizing report.

The history of the study of traumatic shock need only go back to World War I, when a group of illustrious physiologists studied the mechanisms involved in its production. This brilliant work was well summarized in their reports[1, 2] and in the book by Cannon.[3] Many of the physiologic responses that constitute the syndrome of traumatic shock were then delineated, and their cause was ascribed to an assumed but unisolated toxin. Subsequent attempts to isolate the toxin failed.

The period that lay between the two world wars was marked by a reaction against the toxic theory because of convincing studies, largely by Blalock[4] and Phemister,[5] which showed the predominant role of local fluid loss in the areas of trauma. And so we entered this conflict in the wise belief that the treatment for shock is transfusion, and readily available plasma has certainly saved many lives. Nothing I may say in this discussion should be construed in any way as detracting from this brilliant page of medical and, indeed, social progress.

I need not describe to this audience the clinical picture of traumatic shock. It is the delayed collapse that follows lacerating or crushing wounds, characterized by the well-known drop in blood pressure and diminution of blood volume.

With the onset of this war we again set ourselves to evaluate the possibility of toxic causative factors in shock. But why should one study the causes of shock? Surgeons say that there are many causes of this syndrome, but that point of view may change with further knowledge. It is true that the syndrome may develop from anesthesia alone, or that it may appear in relatively mild trauma or may be lacking in larger wounds. The reasons for this have not been clear, which merely proves that we have not yet learned its causes. Although shock may develop under diverse circumstances, true precipitating factors are probably not numerous. Depletion of the blood volume by hemorrhage will produce shock through obvious mechanisms, but shock — the so-called "toxic shock" — can also apparently arise from causes and through mechanisms that are less well understood. It is as true of this syndrome as of any disease that thorough understanding of its mechanisms is essential to logical therapy. Anyone who has observed the effects of bleeding and of trauma in animals or man is alert to the different toxic appearances of the traumatized animal. Something other than the large plasma loss appears to be involved. But this factor has appeared elusive. Moon[6] thought that he had found it by the implanting of autolyzed minced muscle tissue in the peritoneum. Scudder[7] had the ingenious idea that it was due to liberated potassium from traumatized tissues, though we now think that blood potassium rises only late in the shock picture.

The amount of work that has been done in this country on traumatic shock during this war has been large, and our knowledge of the subject is being well advanced. Much of this work is still unpublished and restricted, so that this discussion will be largely limited to recent publications and to our own unpublished data.

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Laboratory studies of traumatic shock have been characterized by the large number of divergent technics and divergent anesthetics in its production. This makes comparison rather difficult. All our observations have been made on dogs with Nembutal given intravenously in amounts sufficient to produce light anesthesia. We have used a new method to produce shock in animals. This was devised as a minimal insult so as not to produce overwhelming shock but to approach the shock state in a more quantitative manner than could be done by technics other than hemorrhage. The method developed by one of our associates, Dr. Nathanson, involves putting tight tourniquets around the two triceps surae, which include the gastrocnemius and soleus muscles. On release of the ties, after five hours, the blood supply becomes re-established and then these muscles swell enormously. The amount of edema that accumulates can be quite accurately estimated by a method, developed by Dr. Kety, of measuring the volume of the limbs.

But fall of blood volume and that of pressure are not the only manifestations of shock that deserve attention. In any experiment it is crucial that other physiologic observations also be made. For blood pressure may be misleading — it may be maintained for a surprisingly long time through vascular constriction, while the shock state may be developing, and then the pressure may fall rapidly, followed promptly by death. Other methods appear essential to judge the early progress of this syndrome — methods that indicate the state of the circulation. Progressive hemic concentration is one of the best technics, as it indicates the actual amount of plasma lost from the circulation. To evaluate the degree of shock we have used technics that originated in the work of one of us (J. C. A.[8-10]) in the last war. It was then shown that when shock is developing the oxygen content of the venous blood is much reduced, that the cardiac output falls, and also that the basal metabolism is reduced owing to the lack of adequate available oxygen. These reactions can all be explained on the basis of a slowing of the blood flow. Our judgment of the degree of shock, therefore, has been based on a fall of cardiac output and blood pressure, a rise in the resistance of the peripheral circulation, mainly that of the arterioles, and a decrease of blood volume. In early experiments we did not obtain all this information, but it has been accumulated in the main body of our recent studies. By means of these technics we were satisfied that we could approach the problem with a quantitative method for producing a minimal shock-producing trauma that would not be so overwhelming as to make study and treatment difficult. We also were able to measure fluid loss in this area progressively, as well as to estimate the beginning and progress of the shock state.

It soon became clear that it would be interesting to study the large amount of fluid that exuded from the anoxic muscles. A technic for this was arranged by enclosing the muscle in a thin rubber sheath from which the fluid could be collected by simple drainage. After the release of the tourniquet and the re-establishment of blood flow through the muscles, fluid fairly poured out into these investing sheaths. These simple operations could all be done with aseptic precautions, and after our first preliminary experiments, the usual surgical aseptic technics have always been employed.

Results

In the first problem we investigated we sought to find whether the shock state produced a changed permeability of body cells remote from the area of trauma, that is, whether the cells of organs such as the intestines and the liver allowed electrolytes and proteins to escape more freely than in a normal state. This was an arduous task undertaken by Dr. Brues, in which Dr. Cohn and Miss Tibbetts helped. These data are ready for publication and need no long discussion here. The conclusion was that there was no indication of any consistent shift of intracellular or extracellular water or electrolytes into or out of cells in shock except what occurred locally in the traumatized regions. In the traumatized areas there was evidence that the permeability of cells was considerably altered, so that extracellular salts were allowed to enter and intracellular salts were abnormally lost. Our experiments, however, have shown other characteristics of fluid exchange that appear interesting and important. At autopsy after prolonged shock one finds the intestinal mucosa full of blood, and Dr. Brues has observed that this appears to be markedly increased by transfusions of plasma or blood, showing that transfused fluids may be lost into this area. This indicates that the permeability of these capillaries has been altered by the shock state and that they therefore lose an abnormal amount of fluid.[11]

It also appears obvious that an abnormal circulation of the body fluids may occur about the area of trauma. Thus, a considerable loss of fluid may exude from the edematous traumatized muscles, sometimes amounting to as much as 200 cc. in five hours. If this fluid is not withdrawn but stays in the legs, it migrates away from the traumatized areas and some of it must be reabsorbed into the circulation. An accessory circulation of fluid is thus established, diffusing through traumatized tissues and being reabsorbed into the general circulation. This may affect the organism as a whole. This circulation, as well as that directly carried in blood vessels and lymph, easily explains the possible widespread effects of the local accumulation of toxic products from trauma. We have established absorption from the anoxic muscle mass by means of radioactive salts. These appear in the blood stream promptly after liberation of the muscle tie.

We have not done this to establish the absorption of the free fluid in the wound, but it could easily be done.

The minimal trauma that I have described produced traumatic shock in about a third of the animals. We then measured the fluid that collected locally from this operation together with the blood that was taken for our various analyses, and compared the incidence of shock in the groups that were subjected to the muscle ties with that obtained in control animals that were bled. There was little difference between the two series. The average indicated that we obtained a somewhat higher percentage of shock in the traumatized animal than in the hemorrhagic controls, but the total loss of blood in the animals that were traumatized was also slightly higher than that of the control animals. From these observations it appeared that the conception of Blalock[4] and Phemister[5] was correct and that the shock of trauma was nothing but a large local loss of fluid. But we were not satisfied with this conclusion because of the somnolence, lethargy and lack of sensibility to pain seen in patients who have suffered trauma, whereas patients who have had simple hemorrhage usually do not exhibit these signs so dramatically.

It appeared desirable to investigate the possibility that edema fluids contained some factor toxic to the organism. We therefore collected the fluid that exuded from the muscles that had been made anoxic. This fluid was easily collected aseptically by our technic, although the amount varied markedly in different animals. By using large animals from which to collect this fluid we could often obtain about 200 cc. from one dog. This slightly hemolyzed fluid could then be put into a small test dog to see its effect on blood pressure, cardiac output, peripheral resistance and hemic concentration. By this technic one was increasing blood volume, not decreasing it. If there were toxic, shock-producing factors in this fluid, it had to compete with this increased volume. Interestingly enough, nine out of thirty-two such fluids produced typical traumatic shock in recipient dogs. The others, however, had practically no effect following injection. Drs. Kety and Pope quite wisely inferred from these observations that the toxic factor in these fluids was not constant, and that it therefore probably arose not from the damaged muscle but rather from some extraneous source. This appeared to confirm the old toxic theory of the last war described in Cannon's book[3] and the more recent observations of Moon.[6]

We were convinced of a toxic element that was sometimes present in the sheath fluid that exuded from anoxic muscle. We therefore attempted to purify this chemically and, for this purpose, collected more than 2000 cc. of this fluid from a series of 9 dogs. It was collected with sterile precautions in bottles cooled in ice and promptly frozen in carbon dioxide snow. These fluids were combined, and the mixture proved to be shock-producing to several dogs. It contained some red cells, the hematocrit being about 1 per cent, had a specific gravity of 1.018 and tended to form a thin clot. An analysis of the inorganic salt content of this fluid showed that it contained much intracellular muscle fluid as well as extracellular fluid, for its potassium content was high and its calcium content low. It also contained less protein and more fixed acid than does blood plasma. The toxic factor in this muscle exudate was found to be a large molecule, for it was not dialyzable and was precipitated in the fraction that contained the protein. In this pool of muscle exudate Dr. Zamecnik also found high concentrations of intracellular proteolytic enzymes, and these enzymes were all contained in the fraction of ammonium sulfate precipitate that contained the toxic factor. We therefore sought to find whether these intracellular enzymes might be the factor that produced shock, but subsequent observations proved to Dr. Zamecnik that this was not so, inasmuch as fresh muscle extract that contained the same enzymes in high concentrations did not produce shock. Laborious attempts at purification, therefore, advanced our knowledge only in so far as they showed that the toxic molecule of this accumulation of muscle exudate was in the protein moiety, possibly in the gamma globulins, that it was destroyed by heat, and that its effects were not due to certain enzymes liberated from the damaged muscle. They did not disclose the actual substance that was producing shock in approximately one quarter of the test animals.

In many of these experiments bacteriologic studies of our muscle exudates were made. It soon became clear that, in spite of strict surgical precautions, all the muscle exudates were infected, most of them with organisms of the gas-gangrene group (in muscle exudates from 19 animals, Clostridia were found in 13, or 70 per cent). Coliform bacilli were not infrequently present, and in a few experiments *Staphylococcus albus* was found. Bacterial contamination was studied quantitatively to obtain an idea of the number of organisms present. Isolated organisms were also studied by Drs. Dubos and Pierce to see whether they produced toxins. The Clostridia were cultured to determine their type and Dr. Dubos's laboratory found them to be the Welch bacillus (*Clostridium perfringens*).

When the number of these organisms was compared with the toxicity of the fluids, it became clear that the three fluids that produced shock in the series were among those that had the highest concentrations of Clostridia. In order to test this finding we assured the presence of an ample infection by injecting a culture of Clostridia into the triceps surae muscles at the time of ligation. In a series of 3 animals we injected Clostridia that had been isolated in previous experiments. These

muscles produced large quantities of fluid in which the amount of organisms varied as the fluid collection progressed. When the resulting heavily infected muscle fluids were injected into recipient animals, they produced profound shock when only one third of the usual amount of fluid was given. Removal of most of the organisms in the injected fluid was accomplished by high-speed centrifugation. The toxic factor did not appear to be the organism, for the supernatant fluid was equally toxic, whereas injected organisms resulted only in producing fever. A single similar observation was described in a report by the British Medical Research Committee[12] during the last war, in which edema fluid from the injection of *Vibrion septique* produced prompt and fatal shock. We next sought an antidote. Polyvalent Clostridia antitoxin was given to a dog a few minutes before injecting an extremely toxic sheath fluid. No shock developed. Our observations indicated that an anoxic muscle was an excellent medium for the growth of Clostridia and for the formation of its toxins.

We became interested in ascertaining why our tissues were so frequently contaminated with Clostridia. A dog's skin was prepared by shaving and thorough scrubbing with soap and water, followed by ether and alcohol solution, and then painting with strong iodine solution. After this strenuous preparation Clostridia could still be found on the intact skin. When Dr. Nathanson used electrosurgical technics with the greatest precaution, Clostridia were still found in the muscles deep in the normal anesthetized dog's leg. We are not sure that they exist there normally, for there is a possibility that spores may be carried into the muscle, but it is clear that they are frequently present in muscles in any traumatizing procedure. Our evidence, as well as confirmatory evidence,[13] demonstrated that Clostridia are practically constantly present deep in the skin of dogs. The presence of Clostridia has been noted before in dog muscles by Roome and Wilson,[14] although they thought them to be nontoxic. It is possible that they do not produce toxins even though they are present in the normal muscle, and that in traumatized muscles they can multiply and produce their usual toxins only in these relatively anaerobic conditions. This discussion becomes only of academic interest in these observations. The important fact is that the organisms are frequently present in traumatized dog muscle, and whether they are normally present or a contaminant makes little difference in the interpretation of our results. Dogs are the animals usually used for the study of traumatic shock, and the contamination of traumatized muscle by these naturally occurring Clostridia appears to us to be significant and to explain our varying cases of shock from muscle juice.

We next turned to the study of purified Clostridia toxins. These were obtained through the kindness of Dr. Milan Logan, who furnished us with the toxins of *Cl. perfringens* and of *Cl. oedematiens*. Injected intramuscularly these toxins produce different reactions. The Welch bacillus (*Cl. perfringens*) produces a great deal of local edema, possibly because its toxin is a lecithinase and therefore has a destructive effect on cell membranes. With this accumulation of fluid in the muscles there develop all the manifestations of shock that we have been determining — a reduced cardiac output, increased peripheral vascular resistance, a fall of blood pressure, a reduced blood volume and its accompanying increased hematocrit, and a lowered venous pressure. All these manifestations may be explained by the local effect of the toxin. We have not yet established whether there is a more general toxic action. When given intravenously this toxin produces marked hemolysis, and although shock is produced, it is different in this regard from our other experiments. We have observed, however, that moderate hemolysis is a common manifestation of shock in dogs, thus confirming the observation of Coonse et al.[15]

Cl. oedematiens toxin does not produce edema promptly when given intramuscularly, and intravenously it results in gradual shock without hemolysis. Following the administration of fatal doses there is often no immediate fall of blood pressure. The cardiac output declines gradually to very low levels, with an increased peripheral vascular resistance. The blood pressure falls terminally. At death there is intense congestion of the duodenum and small intestine, the liver is congested, and the adrenal medulla may be hemorrhagic. These findings are analogous to our pathologic findings in shock, except for the hemorrhagic adrenal glands.

The mechanism is known by which the Welch bacillus produces some of its effects.[16, 17] Macfarlane and Knight[18] showed that the so-called "alpha toxin" is an enzyme — a lecithinase that breaks down lecithin into smaller molecules. Lecithin is a constitutent of cell surfaces, so that destructive effects on capillaries or muscle cells can be understood, as well as the hemolyzing effect on red cells. A change of cell surface usually means a change in cell permeability, and so it is possible to explain the large effusions in the muscles where Welch bacillus toxin is placed. A similar enzyme is present in only small amounts in *Cl. oedematiens* toxin.[19] But this is not the only enzyme, for there is also present another group of enzymes called "hyaluronidases" or mucinases, or the so-called "spreading factor," that hydrolyzes hyaluronic acid. This acid is found in connective tissue, and the enzymic effect of destroying it results in a great increase of diffusibility through tissues and therefore in the spread of extracellular fluid and bacteria. One may thus explain the great edema, not only its presence adjacent to the area of toxin injection but also its widespread diffusion.

Has this work any significance in traumatic shock in the hospital emergency ward or at the front? In a series of eighteen elective orthopedic operations by Dr. Carroll Larsen and others, no Clostridia were found in human muscles. We must therefore decide that any Clostridia present in wounds are introduced at the time of injury. War wounds have been shown to have more than 30 per cent contamination with Clostridia, frequently without the appearance of detectable gas.[20] Such Clostridia, introduced into tissues that have not harbored them before, might be expected to be particularly likely to form toxins. The slow onset of shock seen in some of the wounded agrees with the length of time necessary for the proliferation of bacteria and the formation of their toxins. The importance of such organisms in the shock of war wounds appears to be a problem in regions of combat most urgently needing evaluation.

Our experiments have shown again the great importance of a loss of plasma fluid as a cause of traumatic shock, but they also indicate the importance of infection as a toxic factor. Clostridia that lurk normally in the dog multiply rapidly and produce their toxins in the excellent surroundings of traumatized anoxic muscles. The effects there will certainly accentuate the local fluid loss and so give a summation of effects. The toxin of *Cl. oedematiens* in the blood stream produces a shocklike state, but the mechanism is not yet clear to us. The time relations are satisfactory for allowing organisms to grow and for the onset of delayed traumatic shock. We think that the evidence is quite convincing that infection is the so-called "toxic factor" in traumatic shock in dogs.

We do not know as yet how widespread are the effects of the toxin. In our observations in the shocked animal it is clear that elevation of blood volume by transfusion is followed by markedly accentuated local fluid loss in the upper intestine and liver and lungs, as well as in the area of trauma. Such changes in permeability may be due to simple anoxia or to circulating bacterial toxins. This is a question we are in the process of trying to answer.

There may be other ways to poison the capillaries and venules in the way found characteristic of shock. It is not surprising that long anesthesia should be one such, and that the anoxia of hemorrhage should be another. We have searched hard for other toxins at the area of trauma, but we have not found them. In our experiments, fluid loss and infection appear to account for our incidence of shock. From a practical point of view it is good to have it so, for one can act constructively about them because methods for alleviating them both are available.

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RENAL FAILURE SIMULATING ADRENOCORTICAL INSUFFICIENCY*

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IT HAS been shown that the hormone of the adrenal cortex aids in the maintenance of a normal state of hydration by increasing the renal tubular reabsorption of sodium, chloride and water.[1-4] Hence, in the absence of this hormone, as in Addison's disease, excessive sodium, chloride and water are eliminated by the kidneys and, as a consequence, dehydration, hemoconcentration, hypotension and ultimately collapse may ensue. Theoretically, one might expect to encounter at some time a type of renal tubular damage or incapacity that would prevent the adrenocortical hormone from exerting its usual effect on the tubular reabsorption of sodium and chloride (Fig. 1). Under these circumstances a clinical picture simulating the electrolyte disturbance seen in Addison's disease might be presented by a patient with intact, normal adrenal glands.

Hypochloremia and dehydration have been described in patients with renal disease, and the occurrence of this phenomenon in patients with uremia without edema is well known.[5] To our knowledge, however, the clinical picture of a shock-like state presenting signs and symptoms indistinguishable from those of acute adrenal insufficiency occurring in patients with chronic nephritis and normal adrenal glands has not been reported. The present study is concerned with a report of two patients who, on admission to the hospital, were considered to be suffering from acute adrenal insufficiency. Subsequent studies over a period of two to four years, including post-mortem examinations, proved that the metabolic changes in the body followed renal rather than adrenal disease. These cases are of interest not only because of the physiologic implications that they present but also because therapy directed toward correcting the metabolic disturbances resulted in the rehabilitation of these patients for a life of economic usefulness for periods of two to four years.

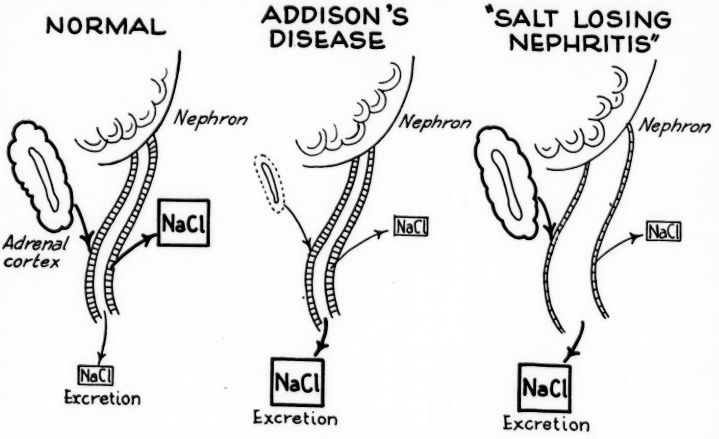

FIGURE 1.

OBSERVATIONS

It is of interest to note the close parallelism that occurred in the clinical courses of these patients.

Both were young adults without clinical evidence of previous renal impairment, and both were admitted in a state of collapse with hemoconcentration, dehydration and hypochloremia. Since protein and formed elements were not present in the urine of either patient, both patients were treated initially with sodium, chloride and glucose solutions as well as adrenocortical hormone in an attempt to correct the apparent acute adrenocortical insufficiency.

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Dramatic improvement followed the therapy outlined above. Following restoration of plasma volume and blood pressure, however, azotemia persisted and kidney-function tests revealed marked and persistent high-grade renal insufficiency. Ultimately, it was shown conclusively that, whereas sodium, chloride and water were lifesaving, adrenocortical hormone preparations were of no value in the treatment of these patients. Sustained clinical improvement — for two and a half to four years — accompanied adequate sodium chloride and sodium bicarbonate therapy. Lastly, moderate hypertension, edema and moderate proteinuria developed terminally in both patients.

Case Reports

Case 1. J. L. (Johns Hopkins Hospital 155764; P. B. B. H. M62361), a 21-year-old man, was admitted to the University of Pennsylvania Hospital on October 18, 1938, complaining of nausea, weakness and vertigo. He had felt well until 1 month prior to admission, when he noted gradually increasing nausea after meals. One week later, he became aware of weakness and vertigo, which was present at first only on exertion but later whenever he was in the erect position. In addition, he had had muscular twitching for several weeks.

At the age of 6 months the patient had a severe throat infection, which was followed by subsequent attacks of less severity. Following tonsillectomy and adenoidectomy at the age of 8, he experienced no further difficulty. There was no history of any other significant childhood illness. His health records at a private school and at a technical school were good. The family history was noncontributory.

During his childhood the patient had noted polyuria and usually had to urinate once during the night. When he was 17 years of age, his appetite became finical. At about that time he found it difficult to arouse himself in the morning because of a sensation of being "doped." In addition, he noted occasional cramps in the legs and feet. A profuse, mucoid postnasal discharge began to manifest itself, and this frequently induced morning nausea and emesis. All these symptoms persisted in varying degree throughout the illness.

Physical examination on admission disclosed a well-developed, freely perspiring young man who appeared chronically ill and evidenced recent weight loss. The blood pressure was 64/46. Generalized sporadic, involuntary, muscular twitchings accompanied by occasional bouts of hiccough were present. The patient was drowsy but aware and intelligent. The skin over the face, body and extremities was markedly freckled, but no abnormal pigmentation was present on the skin or mucous membranes. The axillary and inguinal lymph nodes were slightly enlarged. The ocular fundi appeared entirely normal. There was a uremic odor to the breath. In the right tonsillar fossa a small amount of lymphoid tissue was present. The pharynx was moderately inflamed and a mucoid postnasal discharge was present. The voice was nasal. Examination of the chest revealed no abnormalities. The heart was of normal size, and no murmurs were noted. No abdominal masses or organs could be felt. There was no tenderness in the costovertebral angles. Neurologic examination was not remarkable except for a positive Chvostek's sign.

Laboratory examination at this time disclosed a hemoglobin of 75 per cent and a red-cell count of 4,100,000. Numerous urinalyses disclosed a specific gravity that varied from 1.005 to 1.010. *No albumin or formed elements were present in the urine at any time.* A phenolsulfonphthalein test showed 5 per cent excretion in 2 hours. The blood urea nitrogen was 96 mg. per 100 cc., the serum carbon dioxide combining power 15.0 millimoles per liter, and the chloride 84.8 milliequiv. per liter.

Following the administration of glucose and saline solution intravenously the patient felt greatly improved. Five days later the blood urea nitrogen had fallen to 84 mg. per 100 cc. and the serum chloride had risen to 104.4 milliequiv. per liter. At that time the patient developed a toothache, began to vomit and experienced pronounced malaise. Chemical determinations following the extraction of a badly infected tooth disclosed a rise in the blood urea nitrogen level to 145 mg. per 100 cc., a fall in the serum carbon dioxide combining power to 12.0 millimoles per liter and a fall in the serum chloride level to 88.7 milliequiv. per liter. Administration of adrenocortical extract intravenously, sodium lactate and glucose solution induced temporary improvement. On November 14, the patient was transferred to the Johns Hopkins Hospital.

Physical examination on admission to this hospital was essentially the same as that reported above except that the blood pressure had increased to 96/54 and the patient appeared less acutely ill. The hemoglobin was 10.8 gm. per 100 cc., the red-cell count 2,000,000, the hematocrit (volume of packed red blood cells) 26 per cent, and the white-cell count 4920, with a normal differential count. The serum nonprotein nitrogen was 112 mg., the total protein 6.0 gm., the blood sugar 86 mg., and the cholesterol 190 mg. per 100 cc. An electrocardiogram was normal. Roentgenographic examination of the heart, lungs, gastrointestinal tract (barium meal) and abdomen (flat plate) disclosed no abnormalities.

The patient was given 30 gm. of sodium chloride (1.5 per cent solution) and 10 cc. of adrenocortical extract intravenously each day. Dramatic subjective and objective improvement followed within 2 days. After 4 days on this regimen the blood nonprotein nitrogen was 63 mg. and the total protein 5.9 gm. per 100 cc., the serum sodium 147.2 milliequiv., the chloride 104.8 milliequiv., the potassium 4.9 milliequiv., the carbon dioxide combining power 24.4 millimoles, and the phosphorus 2.6 millimoles per liter. The urea clearance was 10 per cent of the predicted normal. A phenolsulfonphthalein test showed increased excretion to a total of 15 per cent in 2 hours.

It was impossible to state whether the dramatic improvement that had occurred could be ascribed to the administration of the large doses of sodium chloride, to treatment with adrenocortical hormone or to both. To determine more accurately the agent responsible for improvement, the dose of sodium chloride was reduced from 23 to 3 gm. daily for a 5-day period. Despite the continued administration of adrenocortical extract and 20 mg. daily of desoxycorticosterone acetate (a relatively large dose), the previous symptoms of lassitude, nausea and vomiting returned within 2 days. The blood nonprotein nitrogen rose from 65 to 128 mg. per 100 cc.; the serum sodium fell from 145.6 to 131.0 milliequiv., and the serum chloride from 107.8 to 97.2 milliequiv. per liter. The daily administration of 23 gm. of sodium chloride was reinstituted and was again followed by an alleviation of symptoms and a prompt improvement in the chemical findings. At that time the adrenocortical hormone therapy was discontinued. No relapse occurred, and so far as could be determined the patient did as well on sodium chloride therapy alone as he had on the combination of adrenocortical extract and sodium chloride.

The patient was able to leave the hospital for the Christmas holidays, and during this interval he took 25 gm. of sodium chloride daily by mouth without other therapy. On this regimen he was able to be up and about for 12 to 16 hours a day without excessive fatigue. On January 5, 1939, he was readmitted for further study. The blood pressure was 124/80. During this hospital stay he was maintained in good condition with 25 gm. of supplementary sodium chloride daily. The addition to this regimen of 20 mg. of desoxycorticosterone acetate daily (an excessive dose) for 6 days had little effect on the body weight, plasma volume, serum electrolytes and urinary excretion of sodium and chloride (Figs. 2 and 3), in contrast to the striking effect following the administration of a similar dose to patients with Addison's disease and normal human subjects.[6] The administration of 2 cc. (200 units) of parathormone was followed by no increase in the urinary excretion of phosphorus (Fig. 4). Furthermore, Pitressin in doses of 0.25 cc. every 4 hours for a 48-hour period failed to reduce the volume of urine significantly and was not accompanied by any gain in body weight (Fig. 5). Studies of the urinary excretion of ammonia indicated extreme limitation of ammonia formation. Since the carbon dioxide combining power of the blood had gradually fallen from 24.4 to 17.2 millimoles per liter, sodium bicarbonate was given by mouth in addition to supplementary sodium chloride.

During the next 2 years the patient was given large doses of enteric-coated sodium chloride tablets (10 to 20 gm. daily) and sodium bicarbonate (5 to 10 gm. daily), administered orally. He felt well, and despite a persistent gradually increasing anemia and a blood level of nonprotein nitrogen ranging from 70 to 130 mg. per 100 cc., he was able to work full time and occasionally to play golf. Episodes of nausea and vomiting, usually occurring in the morning, were relieved by intravenous infusion of sodium chloride solution, which he obtained at his local hospital en route to work. During this period he frequently returned to the Johns Hopkins Hospital for observation. No great change in the clinical status was encountered, except a slight but progressive increase in the degree of anemia. It was also noted that it became increasingly difficult to induce a significant drop in the blood nonprotein nitrogen level by the administration of sodium chloride solution intravenously.

Additional renal-function tests were carried out during this period in an effort to evaluate the clinical situation and to determine the nature of the underlying pathologic process. All tests performed indicated a marked reduction in renal function. Repeated urea-clearance tests gave values ranging from 5 to 15 per cent of normal. The endogenous creatinine clearance averaged 29.5 cc. of plasma per minute, as compared to a normal of 100 to 120 cc. The sulfanilamide clearance was approximately 12 per cent of the expected normal. The tubular reabsorption (T_m) of glucose was 75 mg. per minute, as compared with the normal rate of over 500 mg. Cold-pressor and mental-effort tests disclosed an active, moderately labile vasomotor system.

In April, 1942, the patient while at work crushed his right thumb, which became infected and failed to heal. Within a month weakness and nausea became pronounced. Because of this the patient was admitted to the Peter Bent Brigham Hospital on July 22.

Physical examination at this time differed from the previous examination as follows. The blood pressure was definitely elevated, being 144/90. Edema of the face and extremities was present. The uremic odor of the breath had increased. The heart, which on all previous examinations had been below normal size, was slightly but definitely larger than normal. Urinalysis showed a fixation of specific gravity (1.008) and a + test for albumin. *No formed elements were noted.* The red-cell count was 1,800,000, the hemoglobin 5.8 gm. per 100 cc., and the hematocrit 24 per cent. The white-cell count was 9300, with a normal differential count. The following chemical findings were noted: nonprotein nitrogen 253 mg., urea nitrogen 187 mg., and total serum protein 5.9 gm. (albumin 3.3 gm.; globulin 2.6 gm.) per 100 cc.; serum sodium 135 milliequiv., chloride 98 milliequiv., carbon dioxide combining power 20.0 millimoles, calcium 3.9 milliequiv., and phosphorus 4.5 millimoles per liter; and alkaline phosphatase 2.3 Bodansky units per 100 cc. The excretion rate of 17-ketosteroids was 1.6 mg. per 24 hours.

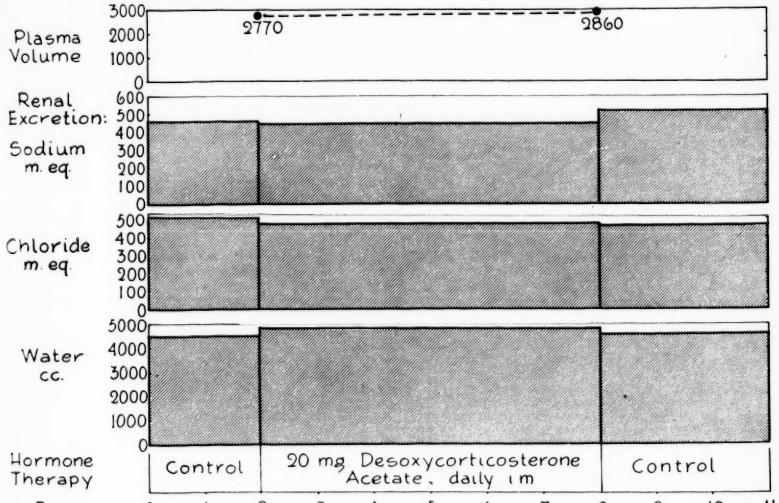

FIGURE 2. *Studies on Sodium and Chloride Balance in Severe Renal Insufficiency During Desoxycorticosterone Acetate Therapy* (*Case* 1).

Because of the presence of edema and hypertension, it was necessary to reduce the dose of sodium chloride. The patient was placed on a high-carbohydrate, low-protein and low-fat diet and was given 5 gm. of sodium chloride and 2 gm. of sodium bicarbonate daily. He was repeatedly transfused. Despite these measures, the course was one of gradual decline. The mucopurulent postnasal drip increased. The blood pressure fluctuated between 130/80 and 164/95. The white-cell count rose gradually to 33,000. The patient became unable to take any appreciable quantity of nourishment by mouth, so that all medication was administered parenterally. The blood urea nitrogen level gradually rose to 304 mg. per 100 cc.; the serum sodium level fell to 124 milliequiv., and the carbon dioxide combining power to 8.0 millimoles per liter. Twenty-six days after admission, the patient lapsed into coma and died.

Autopsy (Dr. S. Burt Wolbach). The body was that of a normally developed but somewhat poorly nourished young white male who appeared to have had a chronic debilitating disease. The skin was pale and of fair complexion; the hair was red. There were ecchymoses, averaging 1 to 2 cm. in diameter, over both forearms and lower legs. The mouth showed a grayish-brown, granular exudate, with an ulcer 1 cm. in diameter on the buccal cavity opposite the last

molar tooth on the right. There was marked pallor of the mucous membranes and slight cyanosis. Examination of the peritoneal cavity showed the kidneys to be somewhat small on palpation but in their usual position. The bladder was distended to the level of the umbilicus and was estimated to contain 750 cc. of urine, which was pale and rather clear. The pericardial surface was smooth, lustrous and without exudate. The heart was somewhat enlarged and reached almost to the midclavicular line. The pleural cavity contained 50 cc. of clear amber solution. The surface was grayish red in color, lustrous and without exudate. The heart weighed 400 gm. and was grossly enlarged, most of the enlargement being noted in the left ventricle. The valves were not dilated. The external contour was of the usual conical shape. On the anterior surface of the left ventricle tures, none of which appeared to communicate with one another. A few submucosal hemorrhages were found in both pelves. The genital organs were normal. The aorta contained a minimal degree of atheromatous change. The superior vena cava and its tributaries were normal. The trachea was normal; the thymus gland was not identified; the thyroid gland weighed 17 gm.; the parathyroid glands were markedly increased in size, the largest measuring 2 by 1 cm. and the smallest 1.5 by 1 cm. Together the four parathyroid glands weighed 5.7 gm.; they were in their normal location and were grayish yellow. The cut surface revealed a tortuous, smooth parenchyma. The lymph nodes were not remarkable. The bones and bone marrow were normal. No abnormalities of musculature were noted.

Microscopically, the renal architecture was markedly

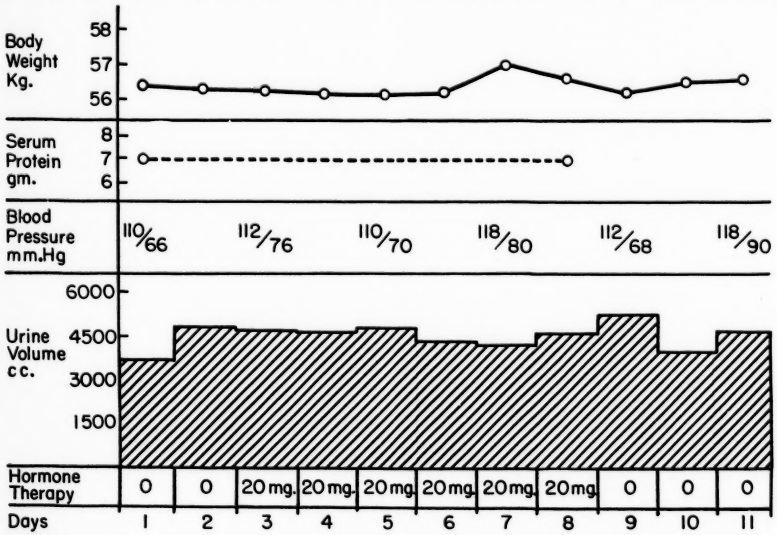

FIGURE 3. *Ineffectiveness of Desoxycorticosterone Acetate Therapy in Renal Insufficiency (Case 1).*

in the region of the apex there were a few small infiltrations of the myocardium with what appeared to be whitish strands of fibrous tissue. Atheromatous changes of a minimal degree were present in the coronary arteries. The lungs and spleen were not remarkable. The alimentary tract was normal except for a few areas of submucosal hemorrhage, from which no actual bleeding point could be demonstrated. The pancreas weighed 95 gm. and was otherwise normal. The liver weighed 1800 gm. and was normal. The gall bladder and ureters were normal. Each kidney weighed 140 gm. No definite abnormalities of blood vessels or ureters were present. Everywhere over the surface were seen cysts varying from 2 to 40 mm. in diameter. The cyst walls were translucent, and yellowish-colored fluid could be seen within the cysts. The kidney capsule was stripped with difficulty. The external surface of the kidney following stripping was of a mottled gray, white and red tissue being interspersed among the various cysts. This tissue was of a finely and uniformly granular appearance. No gross scars were found. The cysts were present throughout the kidney substances, and among them were irregular strands of parenchyma. In general, the cortex was not more than a few millimeters in thickness, but in a few places measured as much as 6 mm. Tubular striations could not be identified. There was great distortion of architecture everywhere; probably four fifths of the surfaces cut in any direction consisted of cystic structures altered by the presence of numerous cystic areas, extensive scarring and extreme dilatation of many of the tubules. There was an irregular increase in the capsular connective tissue. The capsule contained numerous, large, well-filled vascular spaces and in some areas a fair amount of adipose tissue. The inner aspect of the capsule was continuous with the diffuse scarring encountered throughout the renal substance, widely separating the remaining tubules and glomeruli. In many areas it was dense and hyaline, but in others it was fibrillar and appeared to be more recently formed. For the most part, the tubules were lined by low cuboidal or flattened, atrophic epithelium. They were decreased in size and in rare instances contained densely basophilic colloid casts or granular protein material and cellular débris. A striking feature was the separation of the tubules from the capillaries in the scar tissue. Only in a minority of instances did the tubules within the scar tissue closely approximate the capillaries. Many of the latter were well filled with blood elements. Diffusely and irregularly infiltrating the fibrous tissue were moderately large numbers of lymphocytes and plasma cells. Only rare scattered polymorphonuclear leukocytes were present in the interstitial connective tissue.

The glomeruli were decreased in total number in the sections, and those identified showed rather wide variations in size and shape, as well as in the degree of intrinsic glomerular

damage. Throughout the sections were many completely scarred glomeruli, most of which showed scarred adhesions between the fibrosed glomerular tufts and the thickened capsular connective tissue. A fair number of the remaining capillary tufts were only moderately well filled with blood in most instances.

Throughout all the sections there were large areas in which the tubules showed extraordinary dilatation. These were

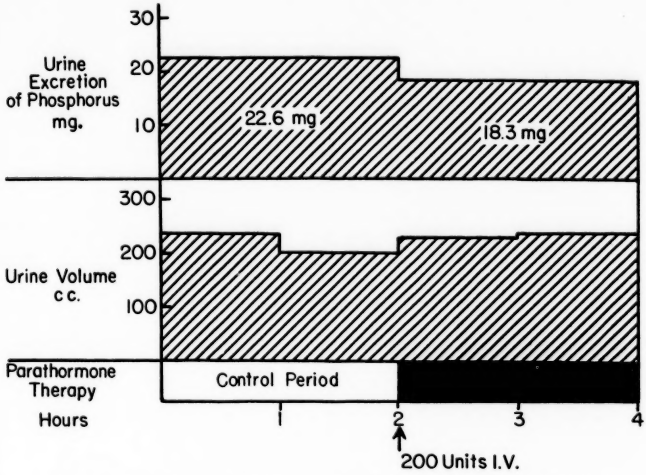

FIGURE 4. *Ineffectiveness of Parathormone Therapy in Renal Insufficiency (Case 1).*

glomeruli showed evidence of past inflammation. There were adhesions between the glomerular tufts and the capsule, as well as some focal scarring in single capillary tufts. For the most part, the pericapsular connective tissue showed lined by moderately low columnar or cuboidal epithelium, but for the most part, they were empty or contained finely granular acidophilic protein precipitate. In some instances, adjacent, greatly dilated tubules appeared to be confluent

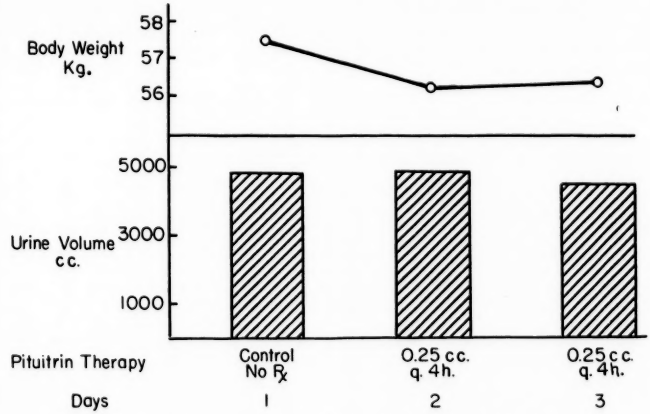

FIGURE 5. *Ineffectiveness of Pitressin Therapy in Renal Insufficiency (Case 1).*

a diffuse laminar thickness. There was no evidence of an active inflammatory process. Only a few glomeruli were free from adhesions or capsular scarring. The residual with the formation of irregular cystic areas. Rarely beneath the tubular membrane there were trapped masses of material that had a basophilic staining tendency and suggested cal-

cium deposition. This was accentuated in the sections stained with hematoxylin and eosin. In several areas, both within the tubules and just beneath the tubular epithelium, there were seen masses of refractile, elongated crystals arranged predominantly in a stellate pattern. For the most part, the scar tissue surrounding the greatly dilated tubules was more fibrillar and better vascularized than that surrounding the atrophic tubules previously described.

Also seen throughout the sections were large cystic areas lined by low cuboidal or flattened epithelium and surrounded by scar tissue. These cystic areas were, for the most part, empty, but a few of them contained fine granules of acidophilic precipitated material. These cysts were encountered in the cortex and medullary regions alike, but the greater number appeared to be just beneath the cortex at the juncture of what in a normal kidney would have been cortical and medullary tissue.

The caliceal and pelvic epithelium included in these sections was fragmentary. Beneath this epithelium there was abundant dense connective tissue that had the lymphoid infiltration seen elsewhere in the kidney substance. The arteries and arterioles showed only slight degrees of intimal thickening and hyalinization. Nowhere was there necrotizing arteriolitis or hemorrhage.

The right adrenal gland weighed 16.5 gm. and the left 24 gm. They were of normal consistence. On section, the cut surface of the adrenal cortex was golden yellow. The medulla was pale gray, and some increase in its thickness was present. No cortical adenomas were noted. The left gland was distorted at one pole, where a large spherical nodule was present. On inspection this did not seem to be a neoplasm.

All sections of the parathyroid glands showed an extraordinary degree of hyperplasia. The hyperplastic cells were in clusters and cords that were separated by delicate reticular connective tissue. In many of the cords the cells were heaped up on each other so that no lumens were present. In many instances, however, the cells were arranged around irregular central lumens. In scattered areas throughout all the sections acinous formation was the predominant feature. In one section a few acini were dilated and filled with acidophilic granular substance. The cell composition of the cords or acini varied from area to area. The predominant cells had clear, colorless cytoplasm and distinct cell boundaries and were moderately large. There were numerous interspersed cells with clear or faintly granular acidophilic cytoplasm. The capillaries coursed in the reticular strands of interstitial connective tissue. Most of these were collapsed and poorly filled. In some areas the interstitial connective tissue was increased in amount and hyalinized, and included in these regions were scattered hemosiderin-laden macrophages. A few moderately large vascular channels were well filled with blood cells. Thin trabeculae dividing the hyperplastic glands in roughly lobular architecture appeared to be derived from perivascular connective tissue.

Case 2. B. P. (Buffalo General Hospital 132264; Johns Hopkins Hospital 230057), a 21-year-old woman, was admitted to the Buffalo General Hospital on February 27, 1940, in coma. She had been in excellent health until August, 1939, when she vomited for the first time. This was followed by repeated attacks of emesis of practically all food ingested. Progressive weight loss and generalized weakness occurred throughout September. The patient felt well during October and November, but in December emesis recurred for 1 week. In February, 1940, the patient again had persistent emesis, became progressively drowsy, and lapsed into coma, at which time she was admitted to the hospital.

The family history was noncontributory. The patient had two siblings who were in excellent health. Her father had a positive serologic reaction but no history, symptoms or physical signs of syphilis.

The patient had had the usual childhood illnesses, but was considered by her parents to have been an unusually healthy child. A tonsillectomy had been performed when she was 12 years old. The blood pressure at that time was normal, and routine preoperative urinalysis revealed no abnormal findings. For 3 or 4 years prior to the onset of her present illness the patient had had nocturia at least once each night. She was the smallest member of her family, and it was thought that she grew less rapidly than her brother and sister. The menstrual history was entirely normal.

Physical examination on admission revealed an acutely ill, emaciated, pale, comatose young woman turning her head from side to side. The rectal temperature was 99°F., the pulse was 120 and weak and thready, and the respirations were shallow and rapid. The blood pressure was 35/0. The skin was dry and the turgor was poor. The eyeballs were soft and the pupils were fully dilated. Examination of the retinal arteries disclosed a slight increase in tortuosity; the fundi were otherwise negative. The chest was clear and resonant. The heart was not enlarged; the rhythm was regular and no murmurs were audible. The heart sounds were distant. The abdomen was soft and no masses were palpable. Pelvic examination revealed no abnormalities. The rectal sphincter tone was good. Knee jerks and ankle jerks were active, and no abnormal reflexes were noted.

Treatment was instituted immediately following admission. Intravenous administration of 5 per cent glucose in physiologic saline solution was begun at once and followed by 1000 cc. of whole blood. The patient was placed in an oxygen tent in the modified Trendelenburg position. The response to this treatment was prompt and dramatic. The blood pressure rose within a few hours to low normal levels and the patient regained consciousness. The following morning (12 hours after admission) she looked and felt greatly improved.

Laboratory examination disclosed a red-cell count of 3,600,000 and a hemoglobin of 7.5 gm. per 100 cc. The white-cell count was 12,350, with a normal differential count. The Kahn and Wassermann reactions were negative. The urine had a specific gravity of 1.010 and a trace of albumin. The chemical findings were as follows: blood sugar 191 mg. per 100 cc.; blood urea nitrogen 249 mg. per 100 cc.; whole-blood chloride 50.8 milliequiv. per liter; serum carbon dioxide combining power 14.1 millimoles per liter, and serum sodium 115 milliequiv., potassium 5.3 milliequiv., calcium 4.1 milliequiv., and phosphorus 6.5 millimoles per liter. The serum albumin was 5.7 gm. and the globulin 1.8 gm. per 100 cc. The whole-blood creatinine was 13.2 mg., the uric acid 8.4 mg., and the cholesterol 156 mg. per 100 cc.

Despite the unusual degree of renal impairment evidenced by the chemical findings, the patient was able to eat fairly well and clinically appeared well. Within 1 week following admission she was up and about the hospital ward. Repeated urinalyses disclosed a fixation of specific gravity at 1.010 and an occasional trace of albumin. *At no time were formed elements present in the urine.* A phenolsulfonphthalein test showed a total excretion of 10 per cent in 2 hours.

Following the administration of liberal amounts of sodium chloride solution the blood urea nitrogen level fell to 195 mg. per 100 cc. and the whole-blood chloride rose to 89.7 milliequiv. per liter. The patient was discharged approximately 3 weeks after admission, feeling reasonably well. At the time of discharge the blood pressure was 100/80.

Following discharge, no specific therapy was given. The patient remained fairly well until May, 1940 (6 weeks later), when she again began to vomit. Emesis occurred in the morning. It became progressively worse and necessitated readmission on June 12. The blood pressure was 106/60, the rectal temperature 99.2°F., the pulse 120, and the respirations 25. The patient was alert. The fundi showed no abnormalities. The remainder of the physical examination was essentially the same as on the previous admission. The outstanding laboratory findings were as follows: red-cell count 3,500,000, and hemoglobin 72 per cent; blood urea nitrogen 264 mg. per 100 cc.; and serum calcium 4.4 milliequiv., serum phosphorus 4.4 millimoles, whole-blood chloride 57.6 milliequiv., serum chloride 71.2 milliequiv., serum sodium 108.7 milliequiv., and serum potassium 4.1 milliequiv. per liter. Repeated urinalyses showed a specific gravity fixed at 1.010, an occasional trace of albumin and *no formed elements.* Roentgenographic examination of the kidney area following the intravenous administration of Diodrast failed to demonstrate the presence of any dye in the renal pelves.

Immediately following readmission the patient was transfused with 500 cc. of whole blood. Four grams of supplementary sodium chloride was given each day. The intramuscular administration of 5 to 10 mg. of desoxycorticosterone acetate daily for a 2-week period had no significant effect on the renal excretion of chloride. Treatment with 16 gm. of sodium chloride and 5 gm. of sodium bicarbonate daily was then instituted. After 8 days on this regimen the patient developed slight peripheral edema and had several convulsive seizures. Chemical examinations at this time re-

vealed a fall in the blood urea nitrogen level to 42 mg. per 100 cc. and a rise in whole-blood chloride to 94.6 milliequiv. per liter. The plasma carbon dioxide combining power was 7.3 millimoles, the serum calcium 5.0 milliequiv., and the phosphorus 2.7 millimoles per liter; the serum albumin was 2.7 gm., and the globulin 1.9 gm. per 100 cc. Treatment was discontinued for 2 days and the convulsive seizures did not recur. The patient was then given 12 gm. of sodium chloride and 3.6 gm. of sodium bicarbonate daily by mouth, and subjective and objective improvement followed. She was discharged in September.

The patient remained relatively well, aside from occasional bouts of morning nausea and vomiting, and was able to do part-time work. Her nausea was controlled by the intravenous administration of physiologic sodium chloride solution. In addition, frequent blood transfusions were given in an effort to correct the anemia. Medication was gradually increased to 15 gm. of sodium chloride and 6 gm. of sodium bicarbonate daily. During that period the blood urea nitrogen level ranged between 73 and 111 mg. per 100 cc. In May, 1941, the patient was admitted to the Johns Hopkins Hospital for further study.

Physical examination on admission disclosed a moderately well-nourished, somewhat underdeveloped young woman. The blood pressure was 128/80. No abnormal skin or mucous membrane pigmentation was noted. The retinal vessels were moderately tortuous, with more than normal shimmer to the retina. The thyroid gland was palpable. The heart was not enlarged. A low-pitched systolic bruit was present over the precordium. The kidneys were not palpable. The extremities were not remarkable. No edema was present. The deep tendon reflexes were hyperactive; there was no Chvostek's sign.

Urinalysis showed a clear urine with a specific gravity of 1.010 and a trace of albumin but *no formed elements*. The red-cell count was 2,700,000, the hemoglobin 8 gm. per 100 cc., the hematocrit 24.1 per cent, and the white-cell count 6400, with a normal differential count. The following chemical findings were noted: nonprotein nitrogen 150 mg., blood urea nitrogen 110 mg., blood sugar 96 mg. and serum protein 7.3 gm. (albumin 5.3 gm. and globulin 2.0 gm.) per 100 cc.; and serum chloride 95.4 milliequiv., the carbon dioxide combining power 21.2 millimoles, potassium 8.6 milliequiv., calcium 4.0 milliequiv., and phosphorus 3.6 millimoles per liter.

Radiographic examination showed the heart to be small and the lungs clear. The long bones appeared normal, but a minimal amount of calcification in the vessels of the lower legs and feet was noted. The kidneys were visualized on a flat plate of the abdomen and appeared small. The electrocardiogram was normal. Various tests of renal function were performed in an effort to elucidate further the nature of the underlying pathologic process. All these tests indicated a high degree of renal failure. The urea clearance was approximately 4 per cent of normal. A phenolsulfonphthalein test showed a total excretion of 9 per cent in 2 hours. The endogenous creatinine clearance was likewise greatly reduced (5.3 cc. per minute per square meter of surface area), and the tubular reabsorption (T_m) of glucose was also markedly impaired. The patient was discharged on May 28. At that time she was taking 12 gm. of supplementary sodium chloride and 6 gm. of sodium bicarbonate daily.

During the remainder of the year, the patient was followed in the Out-Patient Department of the Buffalo General Hospital. She remained moderately well and was able to lead a fairly active life, although occasional bouts of morning nausea and emesis continued to occur. During this period she continued to receive large doses of supplementary sodium chloride medication, which were necessary to allay nausea and to prevent a gradual rise in the blood nonprotein nitrogen level. As time went on, the quantity of sodium chloride solution that induced edema and convulsions became appreciably smaller, so that it became increasingly difficult to maintain the supplementary sodium chloride intake at a level that would alleviate nausea and keep the blood nonprotein nitrogen level from rising.

In January, 1942, the blood pressure had increased to 158/96. The blood urea nitrogen was 130 mg. per 100 cc., the serum chloride 116 milliequiv., the calcium 3.7 milliequiv., the phosphorus 3.0 millimoles and the carbon dioxide combining power 18.5 millimoles per liter, and the total protein 6.1 gm. per 100 cc. The phosphatase content of the serum was 23.6 Bodansky units per 100 cc.

A few weeks later the patient complained of some diminution of visual acuity. Marked edema and punctate hemorrhages were noted in both retinas. The blood pressure had increased to 160/120. The heart was definitely enlarged, and ankle edema was present. Despite a reduction in the dosage of sodium chloride, the edema continued to increase and involved the face and abdominal wall as well as the legs and ankles. The patient was readmitted to the Buffalo General Hospital because of these findings. Despite all measures, her course progressed gradually downhill. Nausea and emesis were more frequent. On March 29, generalized convulsions began. At that time the blood pressure was 180/140, the blood urea nitrogen 144 mg. per 100 cc., and the serum chloride 100.5 milliequiv., the calcium 2.7 milliequiv. and the phosphorus 3.9 millimoles per liter. Following the convulsions, crepitus and swelling were noted over both clavicles. The presence of fractures was confirmed radiographically. Despite the administration of sedatives in large dosage, severe generalized convulsions recurred each day until April 4, when the patient's temperature rose to 107°F. and she expired.

Autopsy (Dr. Kornell Terplan). The body was that of a 154-cm.-long young woman. The entire integument showed a peculiar yellowish-gray coloring. There was distinct edema of the labia majora. The extremities showed slight edema, especially around the ankles. There was also slight edema of both upper arms. The breasts were extremely small and contained little parenchyma. The fat tissue of the breast showed distinct edema. The lower lip was edematous and slightly cyanotic. The teeth were in good condition, as inspected from without, and the gingiva was slightly bluish. The hair was light blond and fairly abundant. The pupils were 5.6 mm. in diameter.

The kidneys appeared markedly shrunken. The right kidney weighed 60 gm. and measured 9 by 3.5 by 3 cm.; the left kidney weighed 42 gm. and measured 7.5 by 3.5 by 2 cm. The capsules were unusually firmly adherent to the cortex. The capsule of the right kidney appeared somewhat thicker than that of the left. On the cut surface, a completely obscured picture was seen. The normal markings had disappeared. The cortex and medulla practically blended into one another, but even so it was apparent that the cortex was markedly atrophic, averaging between 1 and 2.5 mm. in thickness. The color of the cut surface was yellowish pink. No hemorrhages were visible grossly. After the capsule had been removed with great difficulty, the surface had a fairly regular, fine granular appearance, and here and there somewhat yellowish areas were noted near the surface. A few lentil-sized cysts and one hazelnut-sized cyst were present in the right kidney. The left kidney showed exactly the same picture. The fat tissue in the hilus of the kidney appeared relatively increased in amount. The kidney pelvis on each side was of corresponding dimensions. In the right pelvis, there were recent hemorrhages in the mucosa. The gross picture of the kidney was that of diffuse uniform shrinkage corresponding most closely to the late stages of contraction seen in diffuse glomerulonephritis. The branches of the renal arteries were not noticeable, and on section were apparently not thickened or stiffened. The right kidney was duplex, with two renal arteries, which were of normal caliber.

The adrenal glands were of normal size and weighed 7.5 and 8.5 gm. There was considerable lipoid in the cortex. In one gland there were recent capillary hemorrhages in the medulla.

The heart weighed 270 gm. and showed distinct hypertrophy of the left ventricle, which measured 2 cm. in thickness near the bases. The right ventricle measured 5 mm. in the pulmonary conus. The trabeculae of the right side of the heart were fairly prominent. The endocardium in the left atrium showed moderate fibrosis. About 50 cc. of fluid was present in the pericardial sac. The thoracic duct was not remarkable. The foramen ovale was closed. The mitral ostium measured 8.5 cm. in circumference. The aortic valve measured 6 cm. in circumference, the pulmonary valve, 6.5 cm., and the tricuspid, 11 cm. The myocardium was slightly yellowish gray, apparently owing to a slight degree of anemia.

Both lungs showed moderate passive hyperemia and edema. There were fairly diffuse suffusions in the visceral pleura. The parenchyma in both lobes was decidedly consolidated

and dark bluish red. The trachea and bronchi showed marked hyperemia and capillary hemorrhages in the mucosa. The tracheobronchial lymph nodes were small and anthracotic. About 100 cc. of slightly bloody fluid was present in each pleural cavity. Both lower lobes showed superficial atelectasis, especially at the posterior aspects. The thyroid gland was of normal size. The cervical lymph nodes appeared moderately hyperemic. Three parathyroid glands were identified, one of them being slightly larger than normal. The larynx was not remarkable. The thymus gland was present but was considerably reduced in size.

The liver was normal in size and showed distinct passive congestion, edema and slight fatty changes of the peripheral portions. The bile ducts and gall bladder were not remarkable. The gall bladder was thin walled and not edematous and contained yellowish bile. The stomach showed a few coffee-groundlike flecks but no recent hemorrhages. The spleen was of normal size and contained a lentil-sized phlebolith. The pancreas was not remarkable. The entire small intestine showed a peculiar greenish-black discoloration of the mucosa and contained somewhat digested semifluid matter. No hemorrhages were seen grossly. The mesenteric lymph nodes were small, and the colon showed a few petechial hemorrhages near the cecum. There was considerable pseudomelanosis throughout the mucosa of the small intestine. The thoracic and abdominal aorta were not remarkable.

The ribs were thin and cut easily. The cortex appeared somewhat atrophic. The bone marrow was distinctly reduced, and that in the vertebral bodies appeared somewhat anemic.

A variety of sections of the kidneys taken in vertical and frontal planes through the cortex and medulla showed the same picture of marked contraction, with almost all the glomeruli completely or almost completely hyalinized. Considerable hyalinization atrophy of many tubules with practically complete obliteration of their lumens was also noted. The few glomeruli still present were hypertrophic. They showed synechias to the capsule and, here and there, gland-like proliferation of the capsule epithelium. There were rare crescents, but these were for the most part hyalinized. A few glomeruli showed recent dilatation of capillaries, some of them with a considerable accumulation of leukocytes. Some had older hyaline and leukocytic exudate in the capsular space in the process of organization. A few recent capillary thrombi consisting mostly of fibrin and red blood cells were noted. The proximal convolutions were for the most part distended. They showed considerable epithelial desquamation and some fatty droplets. Here and there, erythrocytic, granular and a few small leukocytic casts were noted. The interstitial tissue showed dense infiltration with lymphocytes. The capsule was markedly thickened, infiltrated by lymphocytes and firmly adherent to the kidney. The branches of the renal artery showed only slight thickening of the intima. There was distinct thickening of arteries and arterioles only in the entirely fibrotic areas. In the remainder of the kidney the walls of the small arteries and arterioles were not remarkable. The entire picture corresponded to diffuse glomerulonephritis in the final state, with considerable fibrotic atrophy but still with marked degenerative changes in the somewhat hypertrophic proximal convolutions.

In the parathyroid glands, simple hyperplasia and marked hyperemia were observed. All the cells were so-called "water-clear" cells. Distinct edema was present in the capsules. All sections showed extensive ectasia of capillaries. One parathyroid gland contained a few minute follicles filled with colloid.

The clinical course of these patients is summarized in Tables 1 and 2. The onset of the disease, the clinical and laboratory findings, the response to therapy and the subsequent course of the disease were closely similar in both cases. Both patients were young adults (twenty-one years of age) on admission. The past history in both cases revealed little of significance except long-standing nocturia. There was no history of previous renal disease. The absence of abnormal skin or mucous-membrane pigmentation and the spontaneous hypoglycemia were noteworthy. Routine urinalysis revealed only a slight trace of albumin. No formed elements were present in the urine sediment. Chemical examination of the blood revealed a striking reduction in the serum chloride level and an unusually high nonprotein nitrogen level. The hypotension, the small size of the heart, the absence of vascular changes in the retinal vessels and the essentially normal urine, however, favored a diagnosis of Addison's disease rather than that of uremia secondary to chronic nephritis.

Administration of adrenocortical hormone parenterally, sodium chloride solution intravenously and transfusion was followed by dramatic improvement in both patients. The blood pressure rose to normal levels within twelve hours, and nausea and vomiting ceased. Administration of sodium chloride solution and adrenocortical hormone was continued each day; despite the alleviation of symptoms and the restoration of normal blood pressure and serum chloride levels following this therapy, it was noted that the blood urea nitrogen failed to return to normal. Furthermore, phenolsulfonphthalein excretion was found to be reduced to less than 10 per cent of dye in two hours. These findings, although indicative of high-grade renal failure, did not eliminate the possibility of coexistent adrenal failure. Because of the critical condition of these patients, it was not considered justifiable to discontinue adrenocortical hormone therapy. It was found that both patients were able to tolerate 12 to 15 gm. of sodium chloride and 5 to 6 gm. of sodium bicarbonate daily without developing edema or hypertension, and that on this regimen the serum sodium and chloride concentrations were maintained at normal levels, the blood urea nitrogen level was reduced from 120 to 70 mg. per 100 cc., and both patients were able to lead a life of normal activity. Subsequently, carefully controlled studies revealed that the administration of desoxycorticosterone acetate (synthetic adrenocortical hormone) in large amounts was ineffective in maintaining sodium and chloride balance.

In Case 2, the patient discontinued sodium chloride administration following her initial discharge from the hospital. During the next two months weakness, nausea and vomiting recurred. These changes were associated with a fall in the blood pressure and the serum chloride level (to 71.2 milliequiv. per liter) and a rise in the blood urea nitrogen level (to 264 mg. per 100 cc.). Restitution of supplementary sodium chloride therapy was followed by a prompt remission in symptoms and marked improvement in blood pressure and blood chemistry.

Extensive renal-function tests were performed on both patients in an effort to determine whether the renal lesion primarily represented extreme reduction in all functional elements of the kidney or a specific defect in tubular reabsorption of sodium and

chloride. For details of these tests the reader is referred to the protocols. All tests performed indicated an extreme reduction in functioning renal mass. The degree of renal failure was so great that a valid comparison of the possible differences between glomerular filtration and tubular reabsorption could not be made.

In addition to renal-function tests, experiments were carried out to determine the effect of the administration of hormones whose action is known to be primarily or largely on the renal tubules. The inability of desoxycorticosterone acetate, parathormone and pituitrin treatment to affect the renal excretion of sodium chloride, phosphorus and water, respectively, is demonstrated in Figures 2, 3, 4 and 5. Administration of 20 mg. of desoxycorticosterone acetate daily for six days produced no significant change in the plasma volume or electrolyte balance (Figs. 2 and 3), whereas in normal subjects a striking increase in plasma volume and retention of sodium and chloride was encountered following the administration of 10 mg. of desoxycorticosterone daily.[6] Administration of 200 units of parathormone (Fig. 4) failed to evoke the phosphorus diuresis induced by this hormone in normal subjects.[7] Administration of pitressin (0.25 cc. every four hours) failed to effect a reduction in urine volume (Fig. 5). It is evident from these findings that failure to reabsorb sodium and chloride was not a specific metabolic defect on the part of the renal tubules of these patients. Glycosuria was not observed at any time.

The most striking feature presented by these patients was their ability to tolerate large quantities of sodium chloride (10 to 15 gm. daily) and sodium bicarbonate (4 to 6 gm. daily) without the development of edema and hypertension, in the presence of high-grade renal insufficiency. This phenomenon persisted until one to two months prior to death. It appeared that the ability of the kidneys to reabsorb sodium chloride in excess of water was greatly impaired in both patients, and that the administration of large doses of supplementary sodium chloride was therefore necessary for the maintenance of an adequate plasma volume. Such treatment presented further increase in the level of blood urea nitrogen.

Both patients showed decidedly elevated serum phosphorus levels on all examinations. The serum calcium levels, however, were normal in one patient (Case 1) and definitely below normal in the other (Case 2). It is of interest that latent tetany was usually present in the latter but less frequently so in the former. Involuntary muscular twitchings, on the other hand, were seldom observed in Case 2 but were prominent in Case 1.

In Case 1, the patient was maintained in relatively good clinical condition for a period of nearly four years, and in Case 2 for slightly over two years, by the administration of large doses of supplementary sodium chloride and sodium bicarbonate. The terminal course in the two patients was similar. In each case it was noted that it gradually became increasingly difficult to maintain the sodium

TABLE 1. *Summary of Data in Case 1.*

Date	Blood Pressure	Blood Urea Nitrogen	Therapy: sodium chloride	Therapy: sodium bicarbonate	Body Weight	Edema	Phenolsulfonphthalein Excretion
	mm.Hg.	*mg./100cc.*	*gm.*	*gm.*	*kg.*		*%*
1938: Oct.	64/46	132	*	*		0	5
Nov.	92/68	94	12	0	56	0	15
1939: Jan.	112/80		15	5	58	0	15
Oct.	96/50	129	12	6	55	0	5
1940: Sept.	128/78	109	12	6	56	0	
1941: May	120/70	102	12	6	58	0	9
1942: Feb.	134/90		10	8	57	+	
Aug.	145/90	304	*	*	52	++	

*Intravenous therapy consisting of glucose, sodium chloride and sodium lactate solutions.

TABLE 2. *Summary of Data in Case 2.*

Date	Blood Pressure	Blood Urea Nitrogen	Therapy: sodium chloride	Therapy: sodium bicarbonate	Body Weight	Edema	Phenolsulfonphthalein Excretion
	mm.Hg.	*mg./100cc.*	*gm.*	*gm.*	*kg.*		*%*
1940: Feb.	30/0	249	*	0	36	0	5
Mar.	98/76	127	6	0	37	0	
June	104/62	264	15	5	36	0	5
Sept.	144/92	97	15	5	44	0	
Dec.	128/84	67	16	6	42	0	
1941: June	128/80	102	12	5	42	0	9
1942: Jan.	154/100	76	20	4	42	++	
Apr.	138/100	148	*	*	43	++	

*Intravenous therapy consisting of glucose, sodium chloride and sodium lactate solutions.

chloride intake at a level that would prevent a rise in the blood urea nitrogen level and alleviate nausea and vomiting and yet not lead to hypertension and edema. At the same time, definite vascular changes began to appear in the vessels of the ocular fundi. Terminally, both patients lost ability to tolerate large doses of sodium chloride and developed edema, moderate hypertension and increasing nitrogen retention. The clinical picture changed considerably, so that at death it was perfectly consistent with the usual findings in long-standing chronic nephritis. The immediate cause of death was cardiac failure in Case 1, and uremic convulsions in Case 2.

Discussion

It is our belief that the clinical syndrome that has been described is probably not associated with a typical pathologic lesion in the kidney, but rather occurs late in the course of insidious, slow but progressive renal disease. The slow rate at which the disease progresses and the absence of involvement of all nephrons at any one time permit considerable adaptation to fairly high-grade renal insufficiency. There result extensive scarring, hypertrophy of remaining glomeruli and dilatation of tubules. Under these circumstances the nice balance that normally exists between the quantity of sodium and chloride filtered through the glomeruli and reabsorbed by the tubules is disturbed to the extent that a small excess of sodium chloride is lost daily; ultimately this results in severe depletion of extracellular fluid volume, hemoconcentration and finally increasing renal failure. Increased water intake, without sodium chloride, accentuates the deficiency by increasing urine volume and hence sodium chloride loss.[8] Terminally, with loss or impairment of the few remaining nephrons, the kidney is further limited in its function and both salt and water are retained, resulting in edema, hypertension and cardiac failure. It is our impression that ordinarily few patients live long enough in this precarious balance to reach the stage of severe dehydration and circulatory collapse. A moderate grade of sodium chloride depletion is not infrequently observed in patients with chronic nephritis, particularly when renal impairment is due to healed pyelonephritis, hydronephrosis or vascular nephritis (Peters[5]). It is possible to rehabilitate a number of these patients for periods of months to years by the careful administration of supplementary sodium chloride (1 to 5 gm. daily) and sodium bicarbonate (1 to 5 gm. daily) in conjunction with a large fluid intake (2500 to 4000 cc. daily). The administration of water alone, if it gives rise to a diuresis, may result rather rapidly in sodium and chloride depletion and hence ultimately reduce the volume of extracellular fluid and blood plasma and induce further renal insufficiency.[8] The sodium chloride and sodium bicarbonate must be administered cautiously, in small doses and with due regard for the state of the circulation. Only those patients with adequate cardiac reserve can derive benefit from increasing plasma volume and hence glomerular filtration with sodium chloride and sodium bicarbonate administration. Impending heart failure and excessive hypertension are contraindications to supplementary sodium chloride therapy, even in uremia.

Throughout the present paper merely the level of blood urea nitrogen has been discussed. This has not been done with the idea that the elevated blood urea is necessarily responsible for the clinical symptoms observed in uremia, but rather because in most cases the blood urea level parallels the clinical state.

Summary and Conclusions

A syndrome characterized by excessive loss of sodium, chloride and water, resulting in collapse and associated with renal disease rather than adrenal disease, is described.

Adrenocortical hormone is of no value in correcting the mineral depletion of these patients, since the renal tubular cell on which the hormone normally exerts its effect is unable to respond to additional hormone.

At present there does not appear to be a specific pathologic change responsible for excessive sodium and chloride loss other than widespread renal damage, associated with extensive scarring, a few remaining hypertrophied glomeruli and dilated tubules. Less severe loss of sodium and chloride is not infrequently observed in patients with chronic nephritis, and striking benefit may follow the judicious use of small quantities of supplementary sodium chloride and sodium bicarbonate under these circumstances.

For convenience and for its therapeutic implication, patients with chronic renal disease presenting evident signs and symptoms of sodium and chloride depletion may be said to be suffering from "salt-losing nephritis."

We are indebted to Drs. Richard A. Kern and Francis D. W. Lukens, of the University of Philadelphia, for their kindness in referring Case 1, and to Drs. Clayton W. Greene and Abraham H. Aaron, of the Buffalo General Hospital, for referring Case 2.

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THE PROBLEM OF TUBERCULOSIS CONTROL*

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BOSTON

THE tuberculosis-control problem must be considered as the all-important factor if there is to be a reduction in the mortality and morbidity rate from pulmonary tuberculosis. One is told time and again that pulmonary tuberculosis is becoming a disease of the past and that it is only a matter of several years before it will be entirely eradicated. This is certainly a false notion. To be sure, the death rate in the United States has dropped from 201 per 100,000 in 1900 to 43 in 1940, but it must be remembered that this disease is still the leading cause of death between the ages of twenty and forty. The public is not aware of the magnitude of the present tuberculosis problem. This apparent indifference regarding tuberculosis is shown by the man in the street, who believes, in the absence of tuberculosis in his family, that the problem is nonexistent.

It is apparent from a review of the death rate by occupation, age and sex that the largest numbers of tuberculosis patients are to be found among the underprivileged and low-salaried groups. The huge economic and financial burden of the disease can easily be realized when the cost of long hospitalization is taken into consideration. The taxpayer supports this huge bill, and it is only a matter of time before he will ask for an accounting of these expenditures. That the tuberculosis sanatorium has contributed to the decline in tuberculosis cannot be denied. This contribution can be attributed more to the segregation of positive-sputum cases than to the number of arrested cases. The tuberculosis sanatorium could not possibly justify the expenditure of millions of dollars of the taxpayers' money on the basis of returns to the community in the form of arrested cases.

When it is considered that 90 per cent of the patients admitted to the sanatoriums have advanced disease, it is no wonder that the number of arrested cases returned to society is small. In other words, at present these huge sums of money are being spent yearly for the care and treatment of patients whose disease in 90 per cent of the cases is advanced. It would be a sound investment if more funds could be available for the maintenance of a sound and efficient tuberculosis-control program. By such a program the number of minimal cases would be definitely increased, and at the same time there would be a corresponding decrease in advanced cases.

At the Boston Sanatorium, the number of minimal cases admitted is certainly small (Table 1). It has also been noted that the female patients admitted fall into a lower age group than do the male patients. As would be expected, the age at death in the male patients is higher than that in the female patients (Fig. 1).

Although health departments are usually charged with the responsibility of city tuberculosis control, the sanatorium by virtue of its personnel and equipment should assume a place in the control program. The health department and the sanatorium should work as a single team, hand in hand, to assure success of any tuberculosis-control program. The City of Boston is fortunate in having an efficient health department that is properly and scientifically equipped and conducted. Through its able physicians and public-health nurses, together with its practicing physicians, it is safe to predict that there will be an increase in the number of minimal cases. The participation of the practicing physician is extremely important to a chest-clinic program, especially in the early notification of all cases of pulmonary tuberculosis. In this regard, it should be pointed out that in 1942 there were 388 deaths from pulmonary tuberculosis in Boston, yet only 209 of these occurred in the Boston Sanatorium. The remaining 179 patients must have died either in one of the general hospitals or at home. It is certain that the number that died in general hospitals is very small. It may be added that of the 209 deaths in the sanatorium in 1942, 57 per cent occurred within six months after the patients' admission (Table 2).

TABLE 1. *Stage of Disease on Admission.*

STAGE	1936	1937	1938	1939	1940	1941	1942
Minimal	78 (15%)	55 (10%)	52 (9%)	49 (10%)	46 (8%)	43 (7%)	73 (11%)
Moderately advanced	129	133	165	231	264	394	412
Far advanced	285	314	305	227	241	178	175
Totals	492	502	522	507	511	615	660

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It is unfortunate to see time and again the notification of a case of tuberculosis and the death certificate dated within one or two days of each other. It is obvious that there is an urgent need for more progressive, energetic case finding and early notification.

TABLE 2. *Length of Stay in Sanatorium of 209 Patients Who Died in 1942.*

PERIOD	NO. OF PATIENTS	PERCENTAGE
1–3 mo.	94	44
3–6 mo.	27	13
6–12 mo.	33	16
Over 1 yr.	55	26

It is important to note that the number of patients discharged as apparently arrested, arrested or quiescent is small as compared to the number who are discharged as improved and unimproved, with, in most cases, a positive sputum (Table 3).

TABLE 3. *Condition of Patients on Discharge.*

	1936	1937	1938	1939	1940	1941	1942
Arrested or quiescent	122	202	199	225	172	171	223
Improved	164	112	142	130	163	214	249
Unimproved	13	19	31	24	35	29	41
Nontuberculous	7	6	11	15	15	12	7
Deaths	190	196	170	134	197	168	209
Totals	496	535	553	528	582	594	729

It is a waste of public funds to treat a patient for a few months or weeks and have him leave the sanatorium against advice. A patient of this type is a source of danger not only to himself but also to his family and the community. Many of these patients go to and from the sanatorium at will, with the result that there has been a definite increase in readmissions (Table 4). The State legislators should look into this all-important problem in dealing with the unco-operative tuberculosis patient. Health laws should be strictly enforced in segregating this type of patient.

At the Boston Sanatorium during the last six years there has been an increase in the number of patients admitted, treated and discharged, whereas the average stay of the patient has been reduced (Table 4).

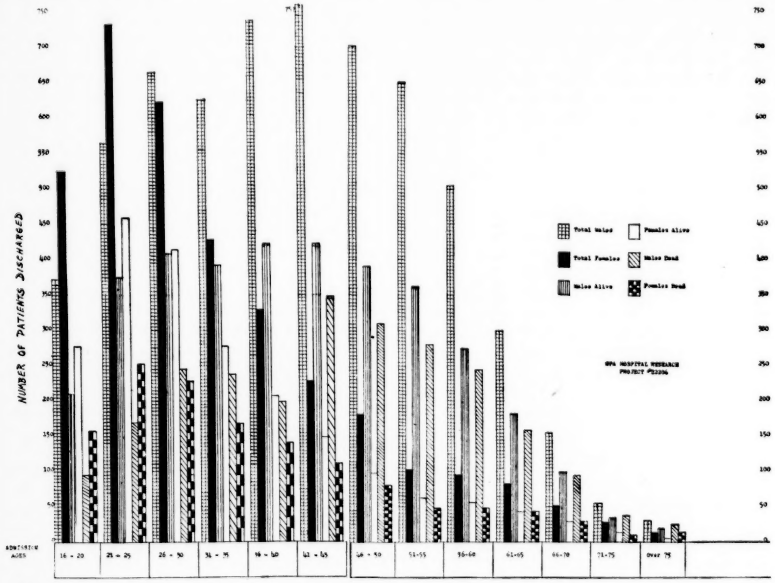

FIGURE 1. *Age Distribution of Patients with Pulmonary Tuberculosis Who Were Admitted to the Boston Sanatorium from 1920 to 1940, inclusive.*

A considerable sum of money should be allotted in educating the public in the problem of tuberculosis.

TABLE 4. *Additional Data.*

	1936	1937	1938	1939	1940	1941	1942
Total patients treated	1079	1088	1082	1042	1070	1110	1180
Readmissions	105	87	127	143	176	158	234
Average stay (in days)	411	426	434	400	352	304	312
Mortality (per cent)	17.5	18.0	15.7	12.8	18.4	15.1	17.7

The public is made somewhat tuberculosis-conscious by the sale of Christmas Seal stamps. The local medical societies should bring the tuberculosis

problem before the public even if it entails employing the radio and cinema.

All high-school children should be given the Mantoux test, and roentgenograms should be taken of all those with a positive reaction. Motorized x-ray field units, each accompanied by a trained roentgenologist and a technician, should be sent into those parts of the city from which most of the cases of tuberculosis come. The Army has aptly shown what can be done by mass x-ray examination. All inductees are examined by means of the 4-by-5-inch photoroentgenogram. It is said that about 1 per cent of all the inductees thus examined were found to have pulmonary tuberculosis. Of these, 90 per cent were found to be in the minimal stage of the disease, and approximately 10 per cent of the cases were classified as advanced. This figure corresponds closely, in reverse ratio, to the minimal and advanced cases admitted to this sanatorium. Many of the larger industrial firms are employing mass x-ray examination of their employees, with profitable results.

A geographic study of the entire city should be undertaken, for it can safely be said that most of the patients in the sanatorium come from certain sections, such as the crowded districts in Charlestown, East Boston, the South End and the North End.

Food handlers should be more carefully checked. It is surprising to see the number of patients admitted to the sanatorium who have been employed as cooks and waitresses.

In addition to the early diagnosis and treatment of pulmonary tuberculosis, it is important to consider the education and rehabilitation of the patient so that he may resume his rightful place in society. This education should be begun as soon as he is admitted to the sanatorium. The adjustment of each patient to his new environment and the solution of his family and economic problems are essential for ensuring a speedy and safe recovery.

Physicians and health units must be taught that post-sanatorium care is just as important as sanatorium care. There is no doubt that the patient will find himself back in the sanatorium unless post-sanatorium care is carefully carried out. It is the duty and obligation of the community to see to it that the patient and his family are well provided for. By so doing the community will realize a profitable return on the investment that has been made.

* * *

In summary, even if it is not possible at present to eradicate pulmonary tuberculosis, owing to its multiple and complex aspects, at least a well-managed and efficient program of tuberculosis control can and should be employed. This will surely bring about a definite reduction in the economic burden, mortality and morbidity rate resulting from pulmonary tuberculosis.

We are indebted to the W.P.A. Hospital Project No. 22206 for the preparation of Figure 1.

MEDICAL PROGRESS

PIGMENTATION OF THE SKIN*

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THE color of the skin of patients is often of distinct diagnostic value. This is true not only for skin disease but also for a wide variety of systemic disorders likely to be encountered in the everyday practice of medicine. Standard textbooks on dermatology offer ready reference for orientation on the primary dermatologic diseases accompanied or followed by pigmentary changes in the skin. By contrast, information relative to the color of the skin in systemic diseases is widely scattered throughout the literature and is often difficult to locate without an extended search. Considerable advance has been made in this field. It is the purpose of this progress report to present a summary and a key to the literature most likely to be available to the average physician. Wherever possible, attention is also called to typical photographs and colored plates contained in these articles. Material for this review has been collected over the last eight years as patients presenting almost all diseases to be discussed were encountered at teaching exercises in the Medical Out Patient Department and on the wards of the Evans Memorial and the Boston City Hospital. During this time information relative to this subject was obtained from the literature, by correspondence or conversation with a number of physicians interested in these diseases and by personal observation of patients.

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Normal Color of the Skin

Many attempts have been made to measure quantitatively and record the color of the skin in disease. An easy method is visual comparison of skin color with a series of color plaques. Rowntree and Brown[1] devised a universal skin tintometer, composed of nine separate color scales resembling somewhat the Tallqvist hemoglobin scale, that allowed evaluation of the skin color of anemia, jaundice, erythrosis, cyanosis and brown pigmentation. These color scales could be analyzed by the Munsell method of color measurement. The methods of Flagg[2] and Lewis[3] (colored plate) for measurement of the degrees of cyanosis and the spinning color top method, widely used in anthropologic study of skin color of racial groups,[4] are other examples. These methods have, however, not been generally used in clinical practice. Almost all physicians evaluate a patient's skin color from visual impression. Knowledge of the causation of normal skin coloration and the pathogenesis of abnormal coloration will place this visual evaluation on a much more rational basis. More attention might be paid to this subject in the courses of applied physiology and physical diagnosis.

A brief summary of the histology of skin will aid in understanding the following discussion of skin pigmentations.[5] From without inward the epidermal layer of the skin (epidermis) is composed of the stratum corneum (keratinized cells), the stratum lucidum (clear acidophilic layer poorly defined except over the palms and soles), the stratum granulosum (a thin layer) and the stratum mucosum (the principal portion of the epidermis), which is attached to the dermis (corium) within and covered by the stratum granulosum without. Its inner surface is indented with papillary processes of the dermis that contain terminal capillary loops. The stratum mucosum is composed of a larger outer prickle-cell layer and a smaller basal layer of two or three rows of cells. Regularly distributed through the basal-layer portion are some clear cells (melanoblasts) that under certain stimuli enlarge, become dendritic and form melanin. Part of the melanin granules are carried outward and can be demonstrated in the outer layers of the skin. The superficial dermis contains cells (chromatophores) that can phagocytize but do not form melanin and that may also phagocytize other pigment complexes — metallic pigments, lipoids and so forth.

The most exact knowledge in this field is based on the spectrophotometric analysis of skin color, an approach pioneered in 1926 by Sheard and his associates.[6–8] Sheard's work allowed skin color to be quantitatively evaluated in terms of relative luminosity, which tells how much of a standard source of light, such as sunlight, the given color is capable of reflecting; dominant wave length or hue, the latter an attribute of color that permits it to be classified as reddish, yellowish and so forth and depends on wave length alone; and purity or saturation, which determines the degree of hue, establishing how vivid or distinct it is. Furthermore, specific absorption changes in spectrophotometric reflection curves enabled actual pigments to be identified. The role of melanin and hemoglobin was especially studied. Much valuable clinical information was obtained from the analysis of skin in disease by this method.[6–8] Williams[9] and Taussig and Williams[10] successfully used an abridged spectrophotometer, which measured the reflected light through three successive filters, in studying the skin color of persons with skin cancer.

Using the Hardy recording spectrophotometer, developed in 1935, Edwards and Duntley[11] were able to study the quantitative distribution of pigments in the normal skin in a manner not possible with earlier instruments and also to identify pigments not previously noted. Briefly, this apparatus

> records the reflectance of the intact living skin, giving an analysis by wave lengths over the entire visible spectrum, from the violet end at 400 millimicrons to the red end at 700 millimicrons. In the curve thus obtained, each pigment is identified by its characteristic absorption band. The amount of the pigment is indicated by the degree of absorption of the wave length of the band. Lowering of the reflectance at the particular wave length is therefore proportional to the amount of the pigment present.[12]

Analysis of normal subjects demonstrated five cutaneous pigments: melanin, a derived material described as melanoid, carotene, reduced hemoglobin and oxyhemoglobin.[11] The color of these pigments was subject to some modification by optical effects produced by the successive skin layers. This fundamental paper is well worth reading in the original.

Carotene

Edwards and Duntley[11] were able to demonstrate that carotene is important in all skin color and is not limited to patients with clinical carotenemia. They recognized the presence of carotene from its characteristic absorption in the blue region of the skin spectrum at 482 millimicrons. Carotene adds a strong yellow component to normal skin color. The normal quantitative bodily distribution of carotene is given in Figure 1, which is reproduced from their paper. It is at once apparent that the classic distribution of the yellow color in a severe case of clinically recognizable carotenemia is essentially an exaggeration of the physiologic normal distribution. Female subjects showed much more carotene throughout the skin than did male subjects. They also showed marked evidence of carotene deposition in the breast, abdomen and buttocks, regions of minimal carotene storage in the male. Carotene was not noted in the scrotum of male subjects, apparently because of complete replacement in this region of the subcutaneous fat by the dartos fibers.

Carotene is normally present not only in dermal and subcutaneous fat but also in the stratum corneum, and in amounts proportional to the thick-

ness of this epidermal layer; hence the prominence of the yellow color of the palms and soles in clinical carotenemia. Sebaceous matter contains a small quantity of carotene. Edwards and Duntley believe that carotene dissolved in the intercellular fluid is transmitted through the stratum mucosum to the stratum corneum. It is stored in the corneum because this layer, by virtue of its lipin content, has an affinity for the pigment, whereas the mucosum,

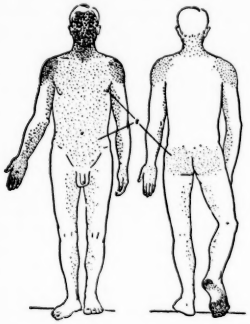

FIGURE 1. *Distribution of Carotene (reprinted from Edwards and Duntley,[11] with permission of the authors and publisher).*

by virtue of a different chemical constitution, possesses no affinity for carotene. A heavy stratum mucosum without much overlying corneum effectively screens the underlying fat without contributing any carotene of its own. This, no doubt, is the explanation for the characteristic lack of yellow in the eyes and mouth of patients with marked carotenemia.

Melanin

Normal melanin pigmentation is of two types. Primary or native pigmentation is controlled by constitutional and racial factors and is responsible for the difference between a brunet and a blond White, the darkness of a Negro and also the regional characteristics exemplified in the normal increase of melanization of skin of the eyelids, nipples and scrotum.[11] Secondary or acquired pigmentation varies with exposure to sunlight and disappears after removal of this stimulus. The pattern of primary pigmentation has been difficult to determine accurately because of the varying degree of secondary pigmentation that all persons acquire. Nevertheless, fairly accurate estimates have been made. Utilizing their own and other available data, Edwards and Duntley have plotted the normal bodily distribution of melanin (Fig. 2). They emphasize that this primary pattern is best exemplified in members of the dark races, in whom the primary melanin layer protects from average sun exposure, and very blond Whites whose ability to react to light stimulus is minimal. The average white brunet always shows some secondary melanin pigmentation (tanning). Some people, especially those with reddish hair and thin skin, manifest melanization in a spotty form (freckles). Melanin is responsible for color effects in the skin varying from yellow through brown to black. The rarity of a predominant yellow melanin lesion in clinical practice has been commented on,[13] but a yellowish-brown hue, as in some types of freckles, is common. The skin of women is generally poorer in melanin than that of men. The female areas of strong primary melanin, such as the nape of the neck, the linea nigra and the axillas, however, show a comparatively higher melanin ratio than do the equivalent structures in the male. Androgens have an apparent role in developing melanin.[12] Hamblen and Cuyler[14] found the average daily androgenic titers of the urine of true blonds to be distinctly lower than those of marked brunets.

It is generally agreed that the color of the skin is a faulty racial test unless correlated with other physical features of the body. Brunsting and Sheard[7] noted that although the percentage of relative luminosity was less from the skin of Negro, Indian, Japanese and Chinese than from that of white persons, the same hue prevailed in all. Edwards and Duntley's[11] study confirmed the idea that the colored races owe their characteristic colors only to varia-

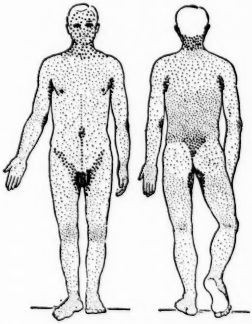

FIGURE 2. *Distribution of Melanin (reprinted from Edwards and Duntley,[11] with permission of the authors and publisher).*

tions in the amount of melanin and, they add, to the amount of the derived pigment melanoid. No pigments other than those found in Whites are encountered in the dark races, and the general plan of the pigment distribution is identical in the two groups. Indians have melanin pigment. The term "redskin" arose from their custom of painting their faces and not to any red pigment contained in the skin.[7]

Melanin is formed by melanoblasts, specialized cells in the basal layer of the epidermis at the junction of the epidermis and dermis. It occurs as microscopic granules in palisade cells of the basal layer of the epidermis, in decreasing amounts toward and including the stratum corneum, with but little in the chromatophores of the corium except in the region of the eyelids and axillas of some persons. It is absent in albinos, present in the smallest amount in blonds, more noticeable in brunets and present in the largest amounts in the darker racial groups.[11, 15]

Melanin is an endogenous body pigment whose mechanism of formation is not clearly understood and is in some respects controversial.[15-25] There is evidence that the metabolism of the amino acid tyrosine is in some way related to its formation. The metabolism of the amino acid phenylalanine is probably also related to pigment metabolism. Under certain circumstances phenylalanine is converted to tyrosine. In vitro studies show that tyrosinase acting with tyrosine forms a melanin-like pigment. Active melanin-producing melanoblasts are believed by many to contain an enzyme (Dopa-oxydase) that causes a dark cytoplasmic color reaction when a fresh section of skin tissue containing them is placed in a solution of dioxyphenylalanin (abbreviated to "Dopa"). A positive Dopa reaction is an indicator of the existence of the faculty of natural melanin production, however, not of the presence of melanin itself. Other epithelial cells and the melanophores of the corium are not Dopa-positive even though they may contain melanin. Controversy still continues concerning the exact meaning of the reaction; nevertheless, the test has much proved merit.[15, 17] Melanoblasts, after having formed melanin, transport the pigment granules to the epithelial cells, and some are phagocytosed by the dermal melanophores. The paths of excretion of melanin appear to be from the skin by desquamation, through the intestinal tract and through the kidneys.[18] Under certain conditions, especially with metastases from melanotic tumors a gross amount may occur in the urine (melanuria). The ingestion of melanin in foods and its synthesis in the intestines may account for much of the pigments in melanosis coli.[18]

The chemical similarity of the amino acid tyrosine to the hormone of the adrenal medulla, epinephrine, the thyroid hormone, thyroxine, and di-iodotyrosine, and of the amino acid phenylalanine to Dopa are worth keeping in mind. Dopa and tyrosinase have not been demonstrated in the human body, but some such similar mechanism for melanin formation is suspected. Melanin metabolism is undoubtedly influenced by pituitary, adrenal and gonadal activity, by the activity of a number of vitamins (A, C and parts of the B complex) and possibly by the nervous system, since some writers believe that parasympathetic predominance stimulates pigmentation formation, whereas sympathetic predominance inhibits it.[22, 25] Many external factors acting on the skin, such as sunlight, artificial ultraviolet rays, x-rays, thorium rays, heat, mechanical irritation and chemical irritation, cause varying degrees of melanin pigmentation. A variable number of these factors, and probably others as yet unknown, may in a complex manner initiate melanin production in disease. It is apparent that analysis of the cause of increased melanin pigmentation in any single case is by no means an easy matter.

Melanoid

Disintegration of melanin particles gives rise to a diffuse pigment in the epidermis, first noted spectrophotometrically in the skin by Edwards and Duntley[11] and named melanoid. Melanoid has, on spectrophotometric analysis, a characteristic absorption, with its maximum slope resembling melanin but shifted from the ultraviolet to the visible violet, thus allowing it to be identified in the spectral reflection curve. They are inclined to believe that it tends to make the skin a yellow of higher purity than does any yellow that can be produced by melanin. The amount in any region depends on the degree of its formation and storage, its formation being related to the concentration of melanin in that particular locality, and its storage to the thickness of the epidermis; the latter is especially true where the stratum corneum (stored dead epithelium) is thick, but holds only to a negligible degree where the stratum mucosum (proliferating epithelium) is heavy and the corneum is thin. Melanoid storage is high in the soles and probably the palms, and minimal in the areas of heavy stratum mucosum in the buttocks, back, cheeks and neck. Furthermore, the turbidity of a thick mucosum causes the optical effect of scattering and raises the blue end of the spectrum, masking the presence of melanoid. For this reason Edwards and Duntley were unable to chart accurately its quantitative distribution.

Oxyhemoglobin

The hemoglobin of blood is present as a varying mixture of oxyhemoglobin and reduced hemoglobin, both of which have such characteristic absorption bands and transmission peaks that recognition of their presence in a spectral reflection curve from the skin is relatively easy. Hemoglobin varies from 90 to 95 per cent oxyhemoglobin in arterial blood to approximately 50 per cent reduced hemoglobin in venous blood. Relative amounts of arterial and venous blood in the skin can thus be determined. Edwards and Duntley[11] found the oxyhemoglobin spectral pattern to be especially prominent in the regions of skin where there is a rich arterial supply and where, for the most part, dermal papillas with their contained capillaries are high. These areas are the red parts of the head and neck, the nipples

the palms, the soles, the region of tuber ischii and the extensor surfaces of the joints. The quantitative bodily distribution of the predominant arterial blood pattern is given in Figure 3.

As is well known, oxyhemoglobin supplies a red component to skin color. Several factors that tend to suppress the oxyhemoglobin bands are present in the skin. The first of these is the increased reduced hemoglobin present in the venous limb of the capillary loop and in the subcapillary plexus with its strong venous blood component. Second, melanin, by its absorption across the spectrum, depresses the entire spectral reflection curve and thus tends to blunt the bands of oxyhemoglobin. This pigment, in proportion to its density, acts as a screen to prevent the superficial blood from attaining visibility. The difficulty of detecting erythema in a dark-skinned Negro is a representative clinical example of this phenomenon. Third, the turbidity of the stratum mucosum overlying the capillary loops adds the optical phenomenon of scattering and raises the blue end of the spectral curve. Brunsting and Sheard's[8] study of the color of bloodless cadaver skin showed the major influence that blood in the superficial capillaries exerts on the color of the skin.

Reduced Hemoglobin

Parts of the body where the papillas are small or absent and where the subpapillary veins are more

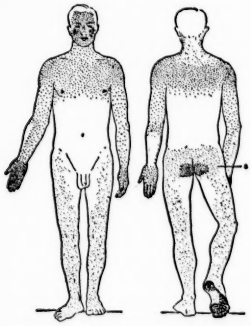

FIGURE 3. *Distribution of Arterial Blood (reprinted from Edwards and Duntley,[11] with permission of the authors and publisher).*

prominent have no special predominance of either form of hemoglobin. Edwards and Duntley[11] denote these areas by the absence of dots (Figs. 3 and 4). In certain areas they noted a real predominance of reduced hemoglobin, probably due to dilated veins and a sluggish flow, as well as the factors minimizing the oxyhemoglobin color that have already been commented on. This phenomenon was marked in the dorsum of the feet, and in the lower parts of the trunk, including the belly, scrotum, loins and buttocks, the last especially in the male. These areas are rich in superficial and comparatively dilated veins, possibly owing to the effect of gravity.

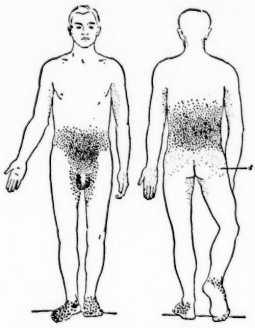

FIGURE 4. *Distribution of Venous Blood (reprinted from Edwards and Duntley,[11] with permission of the authors and publisher).*

Figure 4 contains a diagram of the bodily distribution of these areas.

Reduced hemoglobin adds a blue component to all skin color and becomes predominantly noticeable in true cyanosis.

ANATOMIC AND OPTICAL MODIFIERS OF SKIN COLOR

The color of the skin produced by its five normal pigments is subject to modification by anatomic differences in the various parts of the body surface and the optical effect of the scattering phenomenon. These factors are responsible in part for all skin color, and especially in pathologic conditions in which they may form the mechanism for bizarre and decided variations from normal skin color.

Scattering Phenomenon

The significance of the phenomenon of scattering as a modifier of skin color has been especially emphasized by Edwards and Duntley.[11] Scattering is defined as the rearrangement of light as it passes through a turbid medium; the quantity of light transmitted contains a greater proportion of long wave lengths (red), whereas the light that is scattered to the sides or back to the surface of the medium contains a correspondingly large proportion of short wave lengths (blue). For example, the atmospheric air is a diffuse turbid medium and is responsible for the blueness of the sky at midday and its redness at sunset (Fig. 5). The relatively transparent stratum corneum shows only slight scattering, whereas the turbid stratum mucosum exhibits the phenomenon to a marked degree. All

physicians are familiar with the red color produced by transilluminating living tissue (Fig. 5). They are, however, much less familiar with the importance of the blue color produced by the scattering phenomenon (Fig. 5).

The five skin pigments have in common a preponderant absorption in the blue end of the spectrum, so that were it not for the scattering phenomenon of the normal stratum mucosum, which tends to raise the blue end of the reflected spectrum, the skin would be much redder than it is.[11] Comment has already been made that the blue hue induced by the scattering phenomenon is offset in certain areas by the absorption of the melanoid. Variations in skin thickness, especially of the stratum mucosum, the color is slate gray, and in unusual instances where pigment is deep in the dermis, the color is blue." Other pigments present below the epidermis — silver, iron, carbon and so forth — may cause this phenomenon. It is thus apparent that the same pigment can cause variations in skin color depending not only on the amount present but on the level of the skin at which it is present.

Melanoblasts producing melanin in the corium account for the blue color of the blue nevus[26] and of Mongolian spots[27, 28] (see colored plate[28]). Diffuse melanin pigmentation in the corium may cause the subject to appear diffusely blue,[29, 30] (see colored plate[29]). Pigment deposited in the corium accounts for the blue color of the *taches bleuatres* from the

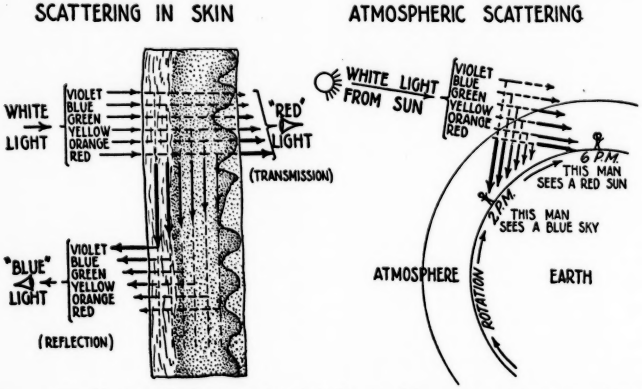

FIGURE 5. *Diagrammatic Representation of the Process of Scattering (reprinted from Edwards and Duntley,[11] with permission of the authors and publisher).*

cause this degree of scattering to vary likewise. The blue color of the larger superficial veins is dependent on this phenomenon. Hemoglobin is present in sufficient quantity to absorb all light striking it. Light cannot pass beyond the vessel into the subcutaneous tissue as it commonly does, so that the usual portion of the total skin reflection from the deeper tissues — predominant red (Fig. 5) — is thus absent. Skin reflection is entirely due to the predominantly blue light reflected from the turbid epidermis and turbid vein wall.

Melanin pigment in chromatophores in the corium if present in sufficient amount behaves in a similar manner, absorbing red rays and reflecting predominantly blue rays so that it appears as blue pigment beneath the skin. Other variations are possible. Becker and Obermayer[15] summarize the color-producing properties of melanin in these words: "When a large amount of melanin is present in the epidermis, the color of the skin is brown, when predominantly in the dermal chromatophores (histiocytes) without too much epidermal pigment, bites of *Pediculosis pubis*,[31] the blue spots produced by hypodermic injections in drug addicts[32–34] who use rusty needles or those with carbon particles from sterilizing in a flame (colored plate[34]); the blue color produced by the black ink used by tattoo artists, the blue color of purpura when free blood is deep in the tissues,[35] probably the blue color of pinta in the pigmented phase and so forth.

Increased melanin in chromatophores probably explains some of the bluish color about the eyelids and in the axillas noted in certain persons. Bluish color caused by pigment in the hair shafts of the shaved male cheek is another physiologic example.[11] A shaved axilla no doubt may likewise show a bluish hue.

Anatomic Variations in Epidermis and Mucous Membranes

The normal epidermis varies in different areas of the body, not only in total thickness but in the relative thickness of each of its component layers. The influence of these normal anatomic variations on

skin color has already been commented on. For anatomical reasons, the color of mucous membrane is quite different from that of the body skin. Any anatomic change in the epidermis or mucous membrane may therefore act to modify its color. In general, thinner epidermis is more transparent and allows the blood in the dermal papillas and superficial dermis to shine through. Thicker epidermis is less transparent and looks yellower.[36]

Variations in Capillary Blood Flow

Capillary blood flow through the skin is not constant but subject to many physiologic variations, causing the color produced by the contained blood pigments to vary accordingly. Brunsting and Sheard[8] give representative examples, such as vasodilatation following change to a warm environment, drinking of alcoholic beverages, local irritation from friction and an emotional disturbance with blushing, all making the skin redder, and vasoconstriction from environmental exposure to cold or the blanching caused by fear, giving a paler appearance. Pathologic processes can also cause profound change in skin color by varying the capillary blood flow.

Edema of Skin

Macerated skin is whiter than normal skin.[15] Likewise, the presence of edema of the skin has a profound influence on skin color, as witness the pallor out of all proportion to the degree of anemia noted in patients with generalized edema of the nephrotic syndrome. Another example is the partial loss of pigmentation noted in some persons with Addison's disease due to the edema caused by desoxycorticosterone therapy and the rapid reappearance of pigmentation when they become dehydrated with the onset of an Addisonian crisis. The influence of edema on the distribution of jaundice in the skin has been especially commented on.[37–39]

* * *

The term "pigmentation of the skin" as used in this review implies a change from normal of the color of the skin, whether due to pigments present in the tissues or to those in the blood passing through the skin. The basic work of Sheard et al.[6–8] and Edwards and Duntley[11] shows clearly that skin color depends on both these factors. It appears to be much more rational and in keeping with physiologic principles always to think of skin color in this manner. Table 1 gives in tabular form a classification of abnormal skin color (pigmentation) that is based on the above physiologic premise. This review primarily considers disorders of general medical interest and for the most part does not include dermatologic disorders. Throughout, attempts have been made wherever possible to crystallize working ideas and clinically useful axioms.

TABLE 1. *Classification of Skin Pigmentations* of General Medical Interest.*

ANATOMIC AND OPTICAL MODIFIERS OF SKIN COLOR
Scattering phenomenon
Anatomic variations in epidermis and mucous membranes
Variations in capillary blood flow
Edema of skin
YELLOW PIGMENTATIONS
Pigmentation of myxedema
Pigmentation of uremia
Dinitrophenol pigmentation
Industrial staining
Picric acid pigmentation
Carotenemia and carotenoderma
Jaundice
Atabrine pigmentation
Local discoloration of abdominal wall:
Cullen's sign
Grey-Turner's sign
Xanthomatosis
Miscellaneous
MELANIN PIGMENTATIONS (see Table 2)
HEMOGLOBIN PIGMENTATIONS
Diminished amount of hemoglobin
Increased amount of hemoglobin
Predominance of oxyhemoglobin
Predominance of reduced hemoglobin
Methemoglobinemia
Sulfhemoglobinemia
Carboxyhemoglobinemia
Cyanhemoglobinemia
Nitricoxidehemoglobinemia
METALLIC PIGMENTATIONS
Hemochromatosis
Hemosiderosis
Argyria
Chrysiasis
Bismuthia
Hydrargyria
Lead pigmentation
Iron pigmentation
MISCELLANEOUS PIGMENTATIONS
Porphyria
Methemalbuminemia
Malarial pigmentation
Pigmentation due to other medicinal agents
Unclassified pigmentations

*As implied here, skin pigmentations may be localized or generalized, and are not primarily related or due to changes in the texture of the skin or to local skin lesions. The term "skin pigmentation" is used to designate changes in skin color due both to deposition of pigments in the skin and to pigments present in the blood.

YELLOW PIGMENTATIONS OF THE SKIN

Carotenemia and Carotenoderma

The work of Edwards and Duntley[11] clearly shows that the pigment carotene contributes a yellow component to the color of the skin of all normal persons. This being so, carotenemia and carotenoderma of clinical significance are merely exaggerations of the normal minimal yellow color of the serum and skin, respectively. This subject was reviewed in detail last year in a progress report of this journal.[40] The yellow of carotenoderma is canary or lemon in hue, in contrast to the bronze, orange, saffron or green tint of jaundice (see colored plates[41]). When clinically significant it is accen-

tuated in essentially the same areas in which it is normally most marked (Fig. 1). Lack of yellow color of the scleras immediately distinguishes it from jaundice (see colored plates[41]). Routine inspection of the palms of patients for yellow color easily suggests this diagnosis. It should be confirmed by the three-layer test of Greene and Blackford.[40]

Jaundice

The aspects of jaundice relative to its influence on skin color appear to be poorly understood. The small amount of bilirubin normally present in the blood and tissues appears to play no detectable role in the causation of normal skin color. It was not detected spectrophotometrically by Edwards and Duntley[11] in their study of the normal skin. The icterus index of blood must therefore increase well over its normal level of 4 to 6, probably well beyond 15 to 25, before it becomes clinically detectable. For the last five years the Fifth and Sixth Medical Services of the Boston City Hospital have performed an icterus index test, using the Wintrobe[42] macroscopic examination of blood, routinely on every patient admitted. Experience has shown that jaundice was readily overlooked on the routine admission clinical examination even when the icterus index ranged over 50. Failure to examine patients with good illumination, preferably daylight, was chiefly responsible. It was the impression that tissue staining (clinically detectable) lagged behind plasma staining (measured by the icterus index) in the early phase of jaundice, the reverse being true as the improvement set in.

The color of the skin in jaundice is variable and has been described as varying from faint yellow through deep yellow, orange, saffron, yellowish green, green and even bronze or dark brown. It is a commonly held clinical belief that the tint of jaundice may be of some diagnostic significance. Some of these tints, as listed in Lichtman's[43] monograph, are orange or saffron in intrahepatic jaundice, greenish to bronze in obstructive jaundice, green in intrahepatic jaundice in the presence of liver necrosis and also in the receding stages of jaundice and olive green in cholangitis and cholangitic cirrhosis. The orange color has theoretically been attributed to bilirubin or the bilirubin pro-pigment, xanthorubin, and the green hue to biliverdin, the oxidation product of bilirubin.[43] Watson's[44] quantitative study of bile pigments has served to place these clinical impressions on a rational basis. Using the Evelyn photoelectric colorimeter he quantitatively measured the amount of biliverdin present in the serum of various types of jaundice. It was not found in pure retention jaundice. Perhaps the absence of biliverdin accounts for the lemon yellow of the retention jaundice of pernicious anemia. In regurgitation jaundice, whatever the cause, some biliverdin was noted regularly. Only in jaundice due to cancer did it exceed 1.0 mg. per 100 cc. Watson's observations were in accord with the clinical impression that outspoken biliverdin jaundice is most frequently due to cancer of the biliary tract. A few marked exceptions were noted in parenchymal jaundice due to subacute or prolonged hepatitis or cirrhosis.

Jaundiced persons who look bronze or brown may have in addition melanin pigmentation. Scratching from pruritus and avitaminosis, both commonly present with long-persistent jaundice, are among the commonest causes for development of melanin pigmentation of the skin.

Wearn[45] has re-emphasized the diagnostic value of a sign but rarely referred to in the modern medical literature. It is described as a yellowish-blue or perhaps greenish color of the skin produced by a combination of the yellow of jaundice and the bluish purple of cyanosis. It is considered almost pathognomonic of an organic tricuspid lesion or a relative insufficiency of the valve. Wearn noted it in 17 of 24 cases. At times, jaundice and cyanosis occur together in other conditions, but their occurrence in other forms of heart disease is not frequent, and differentiation is not difficult.

Jaundice of prolonged duration during infancy may permanently stain with a green color the deciduous teeth forming during this time[46, 47] (see colored plate[46]).

Elastic tissue has a great affinity for bilirubin and is called "bilirubinophilic." This accounts for the ready pigmentation of the skin, sclera, blood vessels and cornea, which are rich in these fibers,[43] and its persistence after other body tissues have cleared. Distribution of these fibers probably accounts for the greater degree of pigmentation noted in the upper parts of the body.[13]

Meakins[37, 38] and others[39] have commented on the absence of jaundice in edematous areas (see colored plate[37]). This curious phenomenon explains the mechanism of the unilateral jaundice syndrome reported by Page,[39] who described it in 2 patients with cardiac failure and hemiplegia. Edema appeared only on the paralyzed side, whereas jaundice appeared on the other side. Jaundice in persons with one glass eye presents, on first glance only, the impression of looking at a person with unilateral jaundice.

A wheal formed by injecting histamine into jaundiced skin increases capillary permeability for bilirubin so that the wheal is yellower than the surrounding skin. The yellowish line bordered by two red lines formed by streaking the skin lightly (icterographia) is a similar phenomenon.[43] These procedures can be used as a simple skin test for latent or mild jaundice.[48–50]

Atabrine Pigmentation

The ability of the widely used antimalaria drug atabrine to produce frequently a yellowish pig-

mentation of the skin is by now known to many physicians. The review by Schechter and Taylor[51] dealing with atabrine pigmentation has served to emphasize the importance of this subject. This pigmentation may closely simulate jaundice and lead to diagnostic error. This is especially true if it persists for months and a different physician than the one who ordered the drug sees the patient some time after this medication was discontinued.

The skin pigmentation is noticeable within three to ten days of beginning oral therapy and may persist for a few weeks to as long as four months after discontinuance of the drug.[51, 52] Parenteral administration of the soluble form of the drug does not eliminate the possibility of pigmentation.[51]

The pigmentation is diffuse and most prominent on the dorsum of the hands, arms and feet. It appears on the forehead and face and may form a golden ring around the mouth.[51] Soni[52] has emphasized that the pigmentation is usually most marked on the exposed parts of the body. It may also be accentuated in the interdigital skin folds and neck creases and under the breasts.[51] No changes occur in the texture of the skin.[52] The color has been variously described as lemon, greenish yellow, golden yellow and turmeric, but in any event a yellow component is clearly evident. A medical officer has described it as "a sickly greenish yellow."

Staining of the mucous membranes has not been emphasized in the printed reports and appears to be less reliable and noticeable than the skin color. Schechter and Taylor[51] emphasize that contrary to the experience of others they have failed to notice any significant discoloration of the scleras, a point that is in accord with the extensive experience of two Army medical officers who discussed this subject with me. Further observations will no doubt settle this question. Martin, Cominole and Clark[53] noted yellowish discoloration of the scleras in experimental animals receiving toxic doses of atabrine (0.1 to 0.2 gm. per kilogram of body weight), but not when the dosage was reduced to 0.05 gm. Perhaps the same phenomenon occurs in human beings. If found consistently, the lack of significant scleral pigmentation would readily differentiate atabrine pigmentation and jaundice. Atabrine pigmentation can be distinguished from carotenemia by the deeper pigmentation of the dorsum of the hands in the former and of the palms and soles in the latter.[51] Yellow staining of the skin from chemicals must naturally be eliminated. Quinine does not cause pigmentation.[52] Plasmochin in toxic doses may cause cyanosis from methemoglobinemia.

Atabrine pigmentation appears to result from deposition of the dye in the skin rather than from a secondary metabolic disturbance or liver damage.[51–53] Hecht[54] demonstrated that the pigment found in animals was fluorescent, which suggested that it was either atabrine or a breakdown product thereof. Atabrine does not cause liver damage except possibly when diminished glycogen reserve from malnutrition is present.[54] Ruge[55] has presented data indicating that chemical and clinical reactions characteristic of hepatic damage in acute malaria return to normal under atabrine therapy. Atabrine pigmentation, if prolonged, may be indicative of accumulation of the drug. Constipation, anemia and exhaustion from infectious disease are believed to augment the intensity and duration of the pigmentation.[51, 52] The more marked accentuation of the pigmentation on the exposed parts of the body has suggested some influence of the rays of the sun.[52]

Tests for hyperbilirubinemia are necessary if concurrent jaundice and atabrine pigmentation are suspected. Schechter and Taylor[51] have outlined a simple laboratory procedure that detects atabrine even if only 0.02 mg. is present in the urine. Hansen[56] has reported on the use of atabrine taken for the purpose of simulating jaundice.

Pigmentation of Myxedema

Descriptive terms such as sallow yellow, yellowish pallor, old-ivory tint, waxy yellow and slightly icteric have been commonly used to describe the color of the skin in myxedema.[57, 58] A malar flush or "a light spot of pink high in the center of the cheeks,"[57] yellowish sallowness of the rest of the face and the presence of edematous, coarse-looking features constitute the characteristic facies of myxedema (see colored plate[59]). The pallor component of the color is readily explained by the high incidence of anemia in this disorder.[58] The myxedematous condition of the skin probably also contributes to the pallor.

The yellow component of the skin color is of special interest. Rarely pernicious anemia coexists with myxedema.[60] Under this and perhaps other exceptional circumstances bilirubin pigment may produce a yellow skin pigmentation in myxedema. In the vast majority of cases, however, this is not the cause. The recent reports by Escamilla[58] and Mandelbaum et al.[61] confirm earlier observations[62] that the yellowish color so frequently noted in myxedema is due to carotenemia, which may occur in this disease even when the amount of carotene in the diet is low. According to Escamilla, the conversion of carotene to vitamin A in the liver is hindered by the depressing effect of the lowered metabolism and tends to improve gradually under treatment with thyroid substance. It is believed by some that the thyroid hormone is antagonistic to vitamin A and governs the rate of its consumption. In hypothyroidism the vitamin A in the serum is normal or low, whereas the carotene is increased. Careful inspection of the palms for a yellow color and Greene and Blackford's three-layer test of the serum should be done routinely in all myxede-

matous patients. Escamilla found carotenemia in 7 consecutive cases of untreated myxedema, and similar findings were noted in 2 cases recently studied at the Boston City Hospital. Carotenemia has also been noted in Simmonds's disease[58] and in castrate and eunuchoid men.[12]

Krantz and Means[63] report 6 cases of myxedema manifesting areas of brownish pigmentation of the skin, more pronounced on exposed surfaces of the body. This pigmentation had appeared coincidentally with, or shortly after, the onset of symptoms of myxedema and cleared up promptly under thyroid administration. There was no pigmentation of the mouth. The description given in this paper is suggestive of chloasma areas of melanin pigmentation. The scarcity of such reports in the literature and the lack of similar descriptions in the current textbooks and monographs strongly suggest that a noticeable degree of generalized or localized melanin pigmentation of the skin in myxedema is not a frequent finding. It may possibly be explained as some fortuitous circumstance in the given case.

Pigmentation of Uremia

The skin in patients with long-standing renal failure is often of a peculiar pale, yellowish, yellowish-brown or buckwheat tint. Anemia undoubtedly accounts for the pallor. Becher[64] believes that, in renal insufficiency, chromogens of urine pigments are retained in the blood and become stored in the tissues and skin. The yellowish discoloration is most pronounced on the face and hands because under the influence of light the chromogens are changed into pigments as the result of oxidative processes. The light color of the urine in patients with uremia is believed to be due partly to retention of chromogens in the blood and in tissues and partly to an inability of the kidneys to oxidize these pro-pigments to pigments.[65]

Boeck and Yater[66] noted carotenoderma in 10 per cent and carotenemia in 100 per cent of a group of kidney cases. It seems likely that carotenemia contributes to the pigmentation of patients with uremia. This has been attributed to poor urinary excretion of the carotenoid pigments, but the extent of urinary loss of carotene normally sustained is by no means agreed on.[66–68]

The brownish tint of the skin noted occasionally in patients with uremia is impressive. Whether any increase in skin melanin occurs is not known. Generalized pruritus is a common symptom in uremia. The resultant scratching irritates and mildly traumatizes the skin. Malnutrition is likewise frequent in uremic patients. These are among the known stimulants for an increase in melanin pigmentation of the skin, which may be additive to and blended with the underlying yellowish pigmentation of uremia. An excess of a hormone of the pars intermedia affecting pigmentation is mentioned as present in uremia.[69] What part, if any, this plays in the pigmentary syndrome of uremia of human beings is not known.

Dinitrophenol Pigmentation

Dinitrophenol is a pale-yellow crystalline powder used as an explosive, in the dye industry and for the preservation of timber. Only the 2-4 isomer has toxic properties. During 1915 and 1916 poisoning of workers in shell-filling factories in France was frequent. Workers showed yellow staining of the face, legs, forearms and especially the palms and soles. Hunter[70] has recently reviewed the clinical features of the mild and severe forms of systemic poisoning. By 1918 industrial precautions were so well developed that dinitrophenol was used with little or no poisoning resulting from its handling.

American physicians became familiar with 2–4-dinitrophenol in 1933, when because of its metabolic stimulating properties it was used for the treatment of obesity.[71] For a time it was widely used for weight reduction, both by prescription and in numerous proprietary preparations. The many reports of toxic reactions from its use led to its general withdrawal as a therapeutic agent. Of interest here was the observation that dinitrophenol often discolors the scleras and even the skin, thus simulating the clinical appearance of jaundice.[72] The discoloration is due to the drug in the plasma and body tissues. It varies from time to time and disappears gradually after ingestion of the drug is discontinued. Since it colors serum and plasma, it may give false high values for the blood icterus index. This can be avoided by determining the index on blood plasma that has been acidified.[72]

Except in rare cases, dinitrophenol does not cause liver damage and jaundice.[72, 73] Liver function is usually normal.[74, 75] The yellow color is purely one of staining tissue and blood. If yellow pigmentation due to dinitrophenol is suspected, the diagnosis can be established on the basis of a history of using a remedy for weight reduction and determination of the icterus index with acidified plasma as compared to nonacidified plasma.

Staining Due to Substances of Industrial Origin

There are a number of chemicals used in certain industries that produce yellow staining of the skin in employees exposed to or handling them. An important one of these is tetryl, or trinitrophenylmethylnitramine, a pale-yellow crystalline powder that is an important ingredient in explosives. Employees handling tetryl powder frequently develop a yellow staining of the hands in one to three days and of the face, neck, scalp and hair in one to three weeks.[76] This color deepens on exposure to sunlight and becomes more prominent during the summer.[75] In industry the terms "canary" and "tetryl blond" are frequently used to describe persons with

this yellow staining of the hair, scalp and face.[76] It is not necessarily indicative of impending dermatitis. Tetryl dermatitis generally occurs between the second and the third week of exposure and is characterized by a burning, itching, erythematous, edematous rash of the circumoral region of the face and the lateral surfaces of the neck, and less frequently of the arms. It is often stated that tetryl produces only these local manifestations. Witkowski et al.[76] stress that systemic symptoms, such as epistaxis, sneezing, nonproductive cough, chest pain, anemia, increased irritability and anorexia, may occur. The presence of yellow staining aids in evaluating patients with industrial exposure. The history of occupational exposure, staining of the hair, the lack of yellow scleras and the fact that tetryl does not cause jaundice enable the physician to recognize readily the significance of the yellow staining.

Other substances handled industrially likewise stain exposed skin surfaces yellow in a manner similar to tetryl. Picric acid,[77] trinitrotoluene (see colored plate[78]), styphnate, nitric acid[77] and the German explosive, hexanitrodiphenylamine,[77] are among the more important ones. In sharp contrast to tetryl, some of these may cause liver damage and true jaundice. Jaundice occurring in an industrial "canary" can readily be overlooked.

Picric Acid Pigmentation

Simulated Jaundice

Judging from the literature appearing during World War I, simulated jaundice as a form of malingering was evidently not uncommon in some of the European armies.[79–84] As a medical curiosity it ranks with the use of egg albumin in the urine to simulate albuminuria and injections of turpentine and paraffin to produce artificial abscesses.[82] Simulated jaundice was produced by the oral ingestion of 5 to 10 cgm. of picric acid three times a day in pill form.[79–82] Within one or two days the skin and scleras became pigmented yellow and on routine clinical inspection the patient could pass as having jaundice. Vomiting, abdominal pain, anorexia, nausea and diarrhea were often noted. The urine was more likely to be orange to red than to have the usual bile-stained appearance, but was sometimes normal in color. A yellow color is due to staining of the tissues by picric acid, or more likely to a breakdown product such as picramic acid. The stain sometimes persisted for several weeks. A similar syndrome has been reported from picric acid absorbed from ointment used to treat an open wound.[79] Numerous tests of the urine and blood were devised to detect the simulation of jaundice from ingestion of picric acid.[79, 80, 82, 83] The practice entailed danger, since picric acid is toxic to the liver and true jaundice from liver damage could be engrafted onto the picture of pseudojaundice.[81, 84]

From the scarcity of reports in the current literature it appears that simulated jaundice has not been encountered during World War II or possibly has not been reported. Hansen[56] reports a case of simulation of jaundice by the use of atabrine.

Local Discoloration of Abdominal Wall

Cullen,[85] in 1919, described the occurrence of a discoloration resembling a bruise at the umbilical area of a woman with a ruptured ectopic pregnancy, and utilized this sign to make the correct preoperative diagnosis. The diagnostic value of the sign was confirmed by Hellendall,[86] Novak[87] and many others.[88] Smith and Wright[88] reviewed the literature in detail in 1935 and concluded that the sign is a rare indication of intraperitoneal hemorrhage. In the foreign literature it is sometimes known as the Hofstätter–Cullen–Hellendall sign.[88] Most frequently it is called Cullen's sign and considered diagnostic of intraperitoneal hemorrhage.

Two phenomena appear to have been described under this sign.[89] One is the bluish discoloration noted when intraperitoneal blood is seen through the thin tissue of an umbilicus, a hernia, an incision and so forth. The production of the bluish color apparently involves the same optical phenomenon as described previously for the blue color of skin veins. The other condition is the discoloration of the subcutaneous tissues about the umbilicus, incisions, near the anterosuperior spine of the ilium and in the loins. The color resembles a bruise; it is bluish at first, then becoming bluish green and finally yellowish (see colored plates[85, 87, 90]). The term "Cullen's sign" should be applied to the latter phenomenon.[88] The changing shades of color have been explained as due to oxidation of blood pigments traveling in the lymphatics connecting the umbilicus or incisional area with the peritoneal cavity.

Grey-Turner[91] recorded similar local areas of pigmentation in 2 patients with hemorrhagic pancreatitis, in one case about the umbilicus and in the other in the loins. Direct action of hemorrhagic pancreatic juice escaping by way of retroperitoneal tissue may have produced the loin pigmentation (see illustration[91]). The term "Grey-Turner's sign" has been applied to this phenomenon especially by English writers. Its value for diagnosis of acute hemorrhagic pancreatitis has been amply confirmed.[89, 92, 93] Fallis[89] reports that in one clinic the correct preoperative diagnosis was made in 3 of 35 cases on the basis of the clinical phenomenon of localized discoloration of the abdominal wall. This sign in acute pancreatitis should not be confused with the cyanosis described by Halsted[94] and others,[93, 95] which may take on a mottled pattern and be distributed irregularly over the surface of the abdomen and even the extremities. It is probably a manifestation of peripheral circulatory collapse.

Yellowish pigmentation about the umbilicus due to rupture of the common bile duct was described by Ransohoff.[96] Other causes of hemoperitoneum besides ruptured ectopic pregnancy may cause this phenomenon. There is some evidence that extraperitoneal spread of blood is responsible for this sign. It has been reported as present without free intraperitoneal blood and often absent with gross hemoperitoneum.[88, 89] This sign can be readily overlooked unless searched for carefully with good illumination.

Miscellaneous Pigmentations

Skin lesions characterized by both a yellow color and a recognizable local gross change in skin morphology should not be confused with the type of yellow pigmentation discussed in this review. A clear orientation in this field is given by Weidman[13] in his review of the many nonxanthomatous skin conditions characterized by a yellow hue, and by Montgomery[97] and Thannhauser and Magendantz[98] in accounting for the many different types of xanthomatous skin lesions. In xanthomatosis, the entire surface of the skin is sometimes tinted a chamois or pale yellow.[99] The whole skin area in so-called "systematized amyloidosis" may be of a waxy coloration.[100] Hansen[56] has commented on the yellow skin color that may result from the use of santonin or acriflavin. The earlier literature has emphasized the yellowish discoloration of the palms noted in persons with typhoid fever and known as "Filipovitch's sign."[99]

A peculiar type of jaundice has been described as being present in the septicemias due to gas-bacillus infections, especially in the post-abortive group. The skin color varies from brownish yellow to mahogany. This color has been attributed to the presence in the plasma of bilirubin, oxyhemoglobin, hematin and methemoglobin.[101]

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30291

PRESENTATION OF CASE

A forty-two-year-old teacher entered the hospital for study.

The patient had been in excellent health until four and a half months prior to entry, when he had an attack of chills, fever, cough, chest pain and rusty sputum. He spent five weeks in a hospital in another city, where he was given various sulfonamide derivatives without much benefit but finally recovered. Following discharge from the hospital he slowly gained 10 pounds. He had an occasional dry cough, but was getting along well until three weeks before admission, when a follow-up x-ray film of the chest taken by his physician showed a persistent lesion in the right upper lobe. He was then bronchoscoped in another city; a biopsy was said to have shown epidermoid carcinoma by one pathologist and squamous-cell metaplasia by another. There was no history of exposure to tuberculosis.

Physical examination showed a well-developed, well-nourished man in no distress. Examination was negative except for slight dullness over the right upper lobe, with increased tubular breathing but no rales.

The blood pressure was 140 systolic, 85 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,680,000, with 14 gm. of hemoglobin. The white-cell count was 9200. A blood Hinton test was negative. The urine was normal. The nonprotein nitrogen was 32.5 mg. per 100 cc.

X-ray examination of the chest (Fig. 1) showed partial collapse of the posterior medial segment of the right upper lobe. Within the area of collapse were several air-bearing areas, such as those seen in consolidation of the lung with an open bronchus. The right lower and middle lobes showed some

*On leave of absence.

compensatory overexpansion. The right leaf of the diaphragm moved somewhat limitedly with respiration. The mediastinum was retracted to the right in the area of collapse. There were no evident hilar lymph nodes, pleural effusion or bone metastases. When compared with the films made elsewhere there seemed to have been some reventilation of the lung since the previous examination.

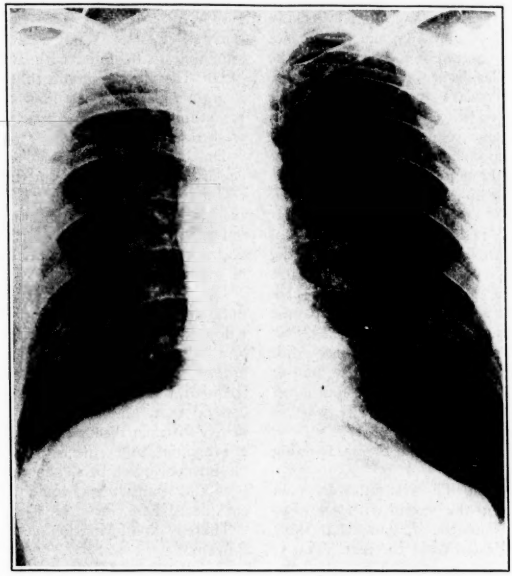

FIGURE 1. *Roentgenogram of Chest.*

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM BECKMAN: I find this case singularly lacking in details that I should like to have in order to make a definite diagnosis. It seems that there can be no doubt, with the initial symptoms four and a half months before admission of chills, fever, cough, chest pain and rusty sputum, that the patient had pneumonia of some sort. These are the characteristic features of pneumonia, and I do not believe anything else could produce that picture, although sometimes a pulmonary infarct may simulate it. I do not suppose that the details of the illness in the other hospital are available, but it would be interesting to know in just what way he did not respond to treatment — whether it was a lack of response of the fever or merely persistence of physical signs for four and a half months.

DR. BENJAMIN CASTLEMAN: They found a Type 2 pneumococcus in the sputum.

DR. BECKMAN: That is helpful because, of course, the presence of a Type 2 pneumococcus in the sputum is uncommon unless it is producing disease. I suspect that it can occasionally inhabit the normal nasopharynx, but in general it indicates infection, which lends further proof to the idea that the patient had lobar pneumonia at the time of admission to the other hospital. Most likely he had a sulfonamide-fast organism or he would have responded better than he did, although we do not know the nature of the course in that hospital. Later, however, he gained 10 pounds to replace some of the weight that he had lost during that illness. Apparently he was in good health, except that the doctor thought he should have a check-up, following which he was advised to come here for study.

It seems to me that one can reason about this case in two ways. The first is that the lesion found at the time of the admission to this hospital was a sequela of the acute infection that he had had four and a half months before. The common complications of pneumonia are, of course, empyema and

lung abscess, which do not seem probable, because he was in excellent health and had no evidence of constitutional disease — no fever and no loss of weight. If he had had a lung abscess and was not producing a large amount of sputum, one would expect fever and general constitutional symptoms. The other possibility along that line is that he developed pulmonary fibrosis, which seems to occur more frequently than we used to think, especially following a primary, atypical pneumonia. The other line of reasoning that one might pursue is that the patient had had some lesion in the lung prior to the illness and that the physical signs were present at that time and persisted through the acute illness without bearing a distinct relation to it. He might have had a benign bronchial adenoma that produced collapse of the lung and acute infection behind the obstruction or he might have had a malignant bronchial tumor. I do not believe that that is likely. There was a rather striking difference of opinion among the pathologists with respect to the biopsy. The clinical picture did not resemble that usually encountered in carcinoma of the lung. He had had no persistent cough and no hemoptysis. Also, if he had had cancer, I should not have expected his symptoms to regress in the way they did; it is more usual for a primary cancer of the lung to have a continuously downhill course. I shall agree with the pathologist who said that there was no malignant disease.

Perhaps Dr. Holmes can help us by interpreting the x-ray films.

DR. GEORGE W. HOLMES: The first film was taken in the usual manner, and the second with a grid to bring out the bronchi and the shadows that show in the lateral view as described in the text. This is typical of collapse of the lung. We have all the signs, namely, decrease in size, increased density in the involved area, displacement of the mediastinal contents toward the affected side, limitation of the respiratory movements of the diaphragm on the affected side and increased brilliancy in the portion of the lung below the affected area. Of course, these are statements made by the one who interpreted the film, and we have to take that into consideration in deciding.

We see here that there is obvious dullness at the right apex. It is not mottled, nor has it the character that one expects to see with old tuberculosis. Then we see along here a dense line that represents the border of the septum, and that is much too high. One can be quite certain that the picture represents a retracted lung; whether that was due to the shutting off of air by something in the bronchus or to a fibrotic process in the lung itself is not too clear. I should think that if it had been due to fibrosis in the lung itself there would be more of the signs of fibrosis in the lung. To me, this looks much more like a collapsed than a fibrotic lung.

Dr. Beckman mentioned the possibility of adenoma. In practically all our cases of benign adenoma the lesion has occurred in one of the large bronchi, not in a small one. This lesion, if it is an obstructing lesion, is not in one of the large bronchi; it would have to involve the small bronchi to produce that appearance. Furthermore, we can see the large bronchi fairly well, and they show no evidence of tumor.

DR. BECKMAN: What about the areas that were supposed to be filled with air?

DR. HOLMES: I should take that statement with a grain of salt. They may or may not represent something. They were possibly areas of lung that were not collapsed.

DR. BECKMAN: That is at least helpful to me, because I feel more secure in the fact that there was real atelectasis. Can you tell whether it was atelectasis or fibrosis? Perhaps that is not a fair question.

DR. HOLMES: My opinion is that it was atelectasis and not fibrosis, but it is not based on a great deal of evidence.

DR. BECKMAN: It is perfectly possible that he had pulmonary fibrosis following pneumonia, although I do not believe that it is likely. I am more in favor of a lesion that occluded some of the bronchi. There are several. I do not know which are the most frequent, but certainly there are various tumors that can do that, and then there is the case[1] that Dr. Helen Pittman discussed here some months ago — a bronchial tuberculosis with a lesion sufficiently large to occlude a bronchus and produce atelectasis. I should think that would have to be seriously considered here.

There is no information on the examination of the sputum.

DR. RICHARD H. SWEET: The sputum was examined a number of times, not here, but elsewhere, and nothing was found.

DR. BECKMAN: I am afraid that I am not sufficiently expert in lung diseases to do anything but guess concerning the nature of this lesion. I am helped a little bit by the fact that an operation was performed. I do not believe that anyone would operate on a patient with pulmonary fibrosis if they were able to make that diagnosis. If I had been handling this case, I should have wanted a bronchoscopy. Possibly that is the operation noted in the record. If anything was learned, it means that the lesion was something that could be seen through the bronchoscope and could be biopsied. As I said before, I have to guess, but shall say that the patient had bronchial tuberculosis, which had occluded one or several bronchi and had produced atelectasis.

DR. J. H. MEANS: Dr. Beckman showed me the abstract of the history this morning. I was interested and looked up in Dr. Lord's book[2] to see what he had to say about lung conditions that

might resemble this. I was particularly interested in what he had to say about the cases of lobar pneumonia that clear up not by resolution but by organization.

There are a number of features that are consistent with this under the heading of subacute and chronic indurative pneumonia. He says, for example, that, when resolution does not take place, but instead there is organization of the exudate, one gets a type of induration that tends to contract, as this had done. He says that it is commoner in cases of pneumonia that have not responded as they should and where the fever has persisted, which is the case here. I was rather intrigued with these areas that might have been cavities, since Dr. Lord speaks of dilatation of the bronchi or cavities in the lung, which may give the breathing an amphoric quality. I therefore mention organizing pneumonia as a possibility in this case. I think that the case hinges on which pathologist was right. One said that he had cancer, and the other that he did not. If he had cancer, he had cancer!

DR. SWEET: I am pleased that this case was discussed here. I had hoped that Dr. Castleman would also present another case, which is a running mate of this one, the patient having been observed continuously at this hospital for a period of five months. The diagnosis was the same in both cases, and both cases were mystifying before operation. Of course one must remember that the patient whose case is discussed here today was sent to me with a diagnosis of carcinoma of the bronchus of the right upper lobe. He and his family had been so informed. He was an apprehensive person and very much worried. It is obvious to those of you who are familiar with carcinoma of the lung that the opportunities to remove small, and perhaps curable, lesions are few and far between. Because I know the man who did the bronchoscopy, I was confident that I could rely entirely on the accuracy of his observation and that we could not have done any better here. So I did not have another bronchoscopy performed. I did get the slides and went over them with Dr. Ronald C. Sniffen, who did not agree with the diagnosis of carcinoma. I therefore made a diagnosis of collapse of the right upper lobe due to obstruction of a process beyond where one could see it with the bronchoscope.

The most frequent cause of that picture, in my experience, is tuberculosis. In other words the usual cause of occlusion of bronchi in the upper lobe is tuberculosis. But I did not believe that this man had tuberculosis. I cannot tell you exactly why. One reason was that he did not have acid-fast organisms in the sputum, and as Dr. Holmes has said, the x-ray picture did not look like that of tuberculosis. I ended up by operating in the hope that I might be getting ahead of an early carcinoma that could not be seen through the bronchoscope. When I got in, there was complete collapse of the right upper lobe, as the x-ray shows. The lobe was densely adherent and exceedingly difficult to get out. In that respect it was very much like the lungs found in many cases of tuberculosis. On the other hand there was difficulty of dissection around the hilus of the lung, which is unlike tuberculosis. I left the operating room still with the impression of tuberculosis, but I did not know whether it was.

CLINICAL DIAGNOSIS

Carcinoma of lung?

DR. BECKMAN'S DIAGNOSIS

Bronchial tuberculosis.

ANATOMICAL DIAGNOSES

Chronic pneumonitis.
Bronchiectasis, slight.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The lobectomy specimen showed a fibrous, rubbery lesion, measuring 10 by 5 by 5 cm., in the anterior portion of the lobe, with a number of dilated bronchi close by. There was no obstruction to the bronchus of this lobe. Microscopic examination of the scarred area showed chronic pneumonitis, with exactly the picture that Dr. Lord described and to which Dr. Means referred. It apparently was an organized pneumonia with a great deal of fibrosis in which there were tiny cavities filled with air, apparently distended respiratory ducts and atria, and a slight degree of secondary bronchiectasis. The whole process, I am certain, was due to the unresolved pneumonia. There was no evidence of tumor or tuberculosis.

DR. SWEET: I would like to emphasize the point which was touched upon before; namely, if one waits in every case for a positive bronchoscopic biopsy in cases of carcinoma of the lung, the opportunity for successful surgical removal is frequently lost. If we are to improve our results in this dread disease, it will be necessary to explore many cases such as this in order to catch a few early cases of carcinoma before it is too late.

This patient left the hospital feeling well; he was much happier than when he came.

REFERENCES

1. Case records of the Massachusetts General Hospital (Case 30152). *New Eng. J. Med.* **230**:468, 1944.
2. Lord, F. T. *Diseases of the Bronchi, Lungs and Pleura.* 632 pp. Philadelphia and New York: Lea & Febiger, 1915. Pp. 264-275.

CASE 30292

PRESENTATION OF CASE

A seventy-year-old Anglican priest entered the hospital because of severe substernal pain.

The patient had been in apparent good health until about two or four months before admission,

when he began to notice chest pain and shortness of breath on exertion, which were relieved by rest. The frequency of these attacks increased. About two weeks before entry, dyspnea and pain first appeared during rest, and in the few days before admission they became almost constant. The pain was substernal and radiated to the left shoulder and to the jaws and was accompanied by a cough.

One year before entry the patient had an unexplained fall, without loss of consciousness, fainting, weakness or visual disturbances preceding or following the fall. Since the age of thirty he had had occasional attacks of agonizing pain in the epigastrium during which he fell to the floor with paroxysms of pain. He could not tolerate fatty foods of any kind. He had not noted clay-colored stools, jaundice or changes in the urine.

Physical examination showed a dyspneic, somewhat icteric and mildly dehydrated man. The neck veins were prominent in a semireclining position. The lower thirds of both lung fields were slightly dull, and many rales were heard on auscultation. The left border of cardiac dullness was 12 cm. from the midline in the fifth space. The sounds were distant. There was reduplication of the second sound in both the aortic and mitral regions. The rate was regular, and there was no pulse deficit. The pulmonic second sound was greater than the aortic. A Grade II apical systolic murmur was heard. The liver edge was palpable one and a half fingerbreadths below the costal margin. Evidence of old varicose vein edema was seen in both lower legs. The dorsalis-pedis pulsations could not be felt. The knee and ankle jerks were absent. The tendon reflexes of the upper extremities were decreased.

The blood pressure was 186 systolic, 120 diastolic. The temperature was 100°F., the pulse 100, and the respirations 25 to 35.

Examination of the blood showed a red-cell count of 4,250,000, with 12.2 gm. of hemoglobin. The white-cell count was 16,600, with 82 per cent neutrophils. A blood Hinton test was negative. The urine was normal. The blood nonprotein nitrogen was 45.5 mg. per 100 cc.

An x-ray film of the chest showed enlargement of the heart in the region of the left ventricle. The transverse diameter of the heart was 16.7 cm., and the inner diameter of the chest 28.5 cm. A moderate amount of fluid was present in both pleural cavities. The hilar shadows were prominent, and the vascular markings were increased throughout both lungs. The aorta was tortuous but not dilated.

The patient was given 0.4 mg. of nitroglycerin, which relieved the pain. He was also given 100 mg. of Demerol intramuscularly and 6 cc. of Cedilanid subcutaneously, followed by 2 cc. in four hours, and he was placed on 0.1 gm. of digitalis daily. An electrocardiogram on the second hospital day showed normal rhythm, with a rate of 110. There was total inversion in Lead 3. The ST segments in Leads 1 and 2 were sagging. The T waves in Lead 3 showed late inversion; Lead 4 looked good.

The patient was unable to sleep or rest because of shortness of breath and substernal discomfort. The anginal pains were fairly well controlled by Demerol. He continued to cough and to raise a small amount of blood. The pulse remained rapid. On the fifth hospital day the lungs showed an increase in the moisture in the bases, and there was some pitting edema of the ankles. He was given 2 cc. of Mercupurin intravenously for two days. The substernal distress seemed to be relieved by sitting up, but his condition continued to fail, and he died on the ninth hospital day.

Differential Diagnosis

Dr. Sylvester McGinn: No single diagnosis that I can think of seems adequate to cover everything in this case, and a number of the symptoms have to be analyzed separately.

First, I should like to speak of the dyspnea, the shortness of breath and pain in the chest coming on with exertion and, a short period of time after that, the shortness of breath at rest. There is no note whether this dyspnea at rest came on suddenly, or whether it occurred in paroxysms, such as cardiac asthma. Later on it is apparent that there was left ventricular weakness, and one might anticipate that there had been cardiac asthma. Then we come to the substernal pain on exertion, relieved by rest and nitroglycerin. Later the pain was constant and came when at rest. Immediately the anginal syndrome is suggested. This man was having midepigastric pain of some severity over a thirty-year period, which occasionally forced him to bend over and fall to the floor. When people assume the knee-chest position and have deep midepigastric pain one thinks of pancreatitis. Since the attacks were repeated, it is quite possible in this case that the patient had chronic cholecystitis with the passage of small calculi, giving biliary colic. We do not know how often these pains occurred, but that is the diagnosis that most adequately covers these attacks.

In the physical examination several features stand out. One thing is definite — the blood pressure of 186 systolic, 120 diastolic. Again, there is evidence that, by percussion, the heart was enlarged in the region of the left ventricle. Other evidence of right-heart strain is shown by increased fullness of the left cervical veins and the fact that the pulmonic second sound was greater than the aortic early, even though the patient had hypertension. We also find that the liver was palpable one and a half fingerbreadths below the costal margin and that there was a moderate grade of jaundice. There are several conditions that could cause acute or even chronic right-heart strain. I am assuming that something happened two weeks prior to entry that was a little different from the previous illness. Pul-

monary infarction would cover all this. People with pulmonary infarction not uncommonly have jaundice, a palpable liver, an increased pulmonic second sound and substernal pain. They also have shortness of breath at rest. One thing to back this up is that there was evidence of varicose veins, which are liable to thrombosis.

I believe that the absent pulsations of the dorsalis pedis arteries were associated with a general arteriosclerotic process. Combined systemic disease, to account for the loss of reflexes, is hardly borne out by a red-cell count of 4,200,000 and an adequate hemoglobin. Some rare condition of the peripheral nerves, such as beriberi or avitaminosis, seems improbable because of the patient's general appearance. He was only mildly dehydrated. A dissecting aneurysm could account for the absence of the dorsalis-pedis pulsations. I am quite certain, however, that if he had had enough of a dissecting aneurysm to occlude the aorta from without, he would have been in shock and unable to maintain a blood pressure of 186 systolic, 120 diastolic. The only characteristic feature of a dissecting aneurysm in this case is the sudden pain in the back. I doubt that that is a cause of lost circulation.

We then come to the x-ray examination, which shows evidence of the fluid of congestive failure, increased lung markings, an enlarged heart and a tortuous and sclerotic aorta. The slightly elevated blood nonprotein nitrogen (45 mg. per 100 cc.) probably goes with a general process of decompensation. The electrocardiogram is interesting if we are considering a diagnosis of angina pectoris, because there is no evidence of coronary occlusion. They speak of sagging in the ST segments in Leads 1 and 2, which is usually considered to be due to digitalis, and of course, this patient had been taking digitalis. The total inversion of Lead 3 was probably due to a high diaphragm, and there was inversion of the T waves in Lead 3, and slight elevation of the ST segments. In fact, this tracing shows very deep T waves in Lead 3. It is difficult to determine how much actual left-axis deviation there is, even in view of the large size of the heart. In view of the total inversion I am not quite ready to think that this single electrocardiogram represents unequivocal evidence of coronary thrombosis.

Apparently the congestive heart failure increased and the patient began to cough up blood. More rales were heard, and it was noticed that the substernal distress, pain as well as shortness of breath, I presume, was relieved by sitting up. I believe that the diagnosis of hypertensive heart disease is justifiable. He had generalized arteriosclerosis, and he had angina pectoris. In addition he had pulmonary infarcts, varicose veins with thrombosis, and chronic cholecystitis and cholelithiasis, which would account for the occasional pain of thirty years' duration.

Dr. Conger W.[illegible]liams: I saw this patient on just one occasion. A[illegible]hat time I wondered whether at least some of his discomfort might have been due to orthopnea, because the statement was made that his pain was much worse on lying down and relieved by sitting up. Although it did not seem likely that all the discomfort was the result of orthopnea, it appeared reasonable that some was due to that as a result of congestive failure. Presumably he was in failure at that time.

Dr. Paul D. White: I saw this man the day before he died. He had been in the hospital a week or so. I never saw a sicker man. He was breathing through an oxygen mask, complaining that he could not stand the discomfort of the substernal pain and of the dyspnea. There was an unusual combination of severe pain and severe dyspnea. He got some benefit from the oxygen, but not enough to give him real relief. There was obviously a good deal of pulmonary congestion, and the question arose, as discussed by Dr. McGinn, whether a pulmonary infarct superimposed on hypertensive and coronary heart disease was the better answer than a myocardial infarct. The electrocardiogram was taken on the second day, and several more days had elapsed before I saw him.

Dr. Benjamin Castleman: He died on the ninth day.

Dr. White: Yes; I saw him on the eighth day, and as I have said, the only electrocardiographic record was taken on the second day. It was essentially negative except for sagging of the ST segments. That could be ascribed to digitalis, but the report is inadequate. This case is an illustration of the need of serial electrocardiograms and of more extensive precordial electrocardiograms in order to be more confident about the diagnosis. I asked for a second record when I saw him, but the patient died before it could be obtained. It would have been important to have had serial electrocardiograms or some precordial records, because one sometimes sees a normal Lead 4, perhaps taken a little inside the apex, and a very abnormal electrocardiogram in positions CF_5 and CF_6.

Dr. Chester M. Jones: Was anything done about esophageal electrocardiograms? Is there any indication for them in patients not so sick as this man in whom there is doubt about coronary disease?

Dr. White: It is still largely a technic for experimentation, although certainly a posterior infarct may be demonstrated in that way. It would have been too difficult a procedure, and I expect not possible, in this patient. We still have an occasional chance to pick up posterior infarction by the precordial leads when recorded early or better still by serial limb leads.

Clinical Diagnoses

Myocardial infarction.
Pulmonary edema.

Dr. McGinn's Diagnoses

Hypertensive heart disease.
Arteriosclerosis, generalized.
Angina pectoris.
Pulmonary infarcts.
Thrombosis: leg veins.
Chronic cholecystitis and cholelithiasis.

Anatomical Diagnoses

Coronary thrombosis, recent, right.
Myocardial infarction, recent: left ventricle.
Pericarditis, acute, fibrinous.
Cardiac hypertrophy, hypertensive type.
Pulmonary edema and congestion.
Hydrothorax, bilateral.
Peripheral edema, slight.
Arteriosclerosis, generalized.
Cor pulmonale?
Pulmonary atelectasis, bilateral.
Esophageal varices.

Pathological Discussion

Dr. Castleman: The autopsy showed a heart weighing over 600 gm., with an enlarged left ventricle and a thick right ventricle, measuring 6 mm.

Dr. White: That would help to balance the electrical axis. In other words, it is possible that he had enough left ventricular failure to give him some right ventricular hypertrophy, or there may have been some other cause in the lungs.

Dr. Castleman: The medium-sized arteries in the lungs were definitely hypertrophied, but there was no cause that we could find for that.

In the heart there was an extremely large posterior infarct involving the apex; this must have been quite recent because of a large number of polymorphonuclears within it, but organization was progressing.

Dr. White: How old was it? A few days, or older?

Dr. Castleman: About two weeks.

Dr. White: It was probably present when he entered the hospital?

Dr. Castleman: Yes. The cause of the infarction was a large thrombus of the right coronary artery, beginning about 5 cm. from the origin of the artery and measuring 6 cm. in length. It was one of the longest coronary thrombi that I have seen.

Dr. White: I suppose that with the progression of this infarct, one might have expected an inversion of T_2.

Dr. Castleman: The gall bladder was normal. The lungs showed atelectasis in addition to moderate medial hypertrophy of the small arteries. I do not suppose that the process was extensive enough to call Ayerza's disease, but it probably accounted somewhat for the right ventricular hypertrophy.

Dr. Jones: Was there any other evidence of previous thrombosis?

Dr. Castleman: The coronary arteries showed extreme sclerosis, such as one sees in patients with angina.

Dr. White: Was there any explanation of the pain in the epigastrium?

Dr. Castleman: No. We found nothing in the gastrointestinal tract except four or five varices in the lower end of the esophagus, with no cirrhosis; the cause of the varices was undetermined.

Dr. Jones: That is impressive because it is rare to find so-called "congenital varices," or I suppose a better term is "varices, cause unknown." I do not believe that they would give symptoms. There was no difficulty in swallowing. That is an interesting anatomical finding without explanation. He did not have a hernia?

Dr. Castleman: None that was apparent. Unless definitely looked for, however, a hiatus hernia can be easily overlooked.

He had acute pericarditis secondary to the infarction. Do you think that might affect the electrocardiogram, Dr. White?

Dr. White: There was not enough wrong in his one record to suspect it.

Dr. McGinn brought up the matter of hypertension and that is one point to which attention should be called. The blood pressure often comes down during pain from acute myocardial infarction, but not infrequently the reverse is true, and occasionally we have seen a higher pressure then than at any other time, either before or after.

Dr. Jones: How long does it persist after thrombosis has taken place — twenty-four to thirty-six hours?

Dr. White: It subsides in a few hours or in a day or two; but it is a point that may lead one astray if one always expects a drop in blood pressure in coronary thrombosis.

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ANNUAL MEETING OF THE AMERICAN MEDICAL ASSOCIATION

After an interval of two years the American Medical Association again held its annual meeting, this time in Chicago on June 12, 13, 14, 15 and 16. In spite of the difficulties of travel and anxieties at home the registration was about normal. The section meetings were, for the most part, crowded. The programs were varied and interesting. Although the scientific exhibit was perhaps not quite so large as usual, it maintained its usual standard.

The House of Delegates convened on Monday, with an attendance of 170 out of a possible 175. The secretary of the Association again reported an increase in membership. There are now 124,452 members, against 122,741 in 1942. Deaths of members have increased, however, there having been 2019 during the year. About half these deaths were due to some form of cardiac disease and about half the cardiac deaths were caused by disease of the coronary arteries. This perhaps is an indication of the tempo at which civilian physicians are now working.

The House listened to reports of its officers, the Board of Trustees and the various councils and committees. The address of the president, James E. Paullin, should be read with care. It gives an idea of the vast amount of work being done by various unpaid committee members during these trying times, in spite of all they have to do in their own practices. His closing remarks were a plea for unity within the organization:

> It is only by the development of complete unity and support that the views of the medical profession, which have been developed for the best interests of the public and for the advancement of science, can be made to prevail. If the purposes and ideals and desires for which we as a medical profession stand are worth while, then there should be the loyal support of every member of all organizations to see that they prevail.

Dr. Herman L. Kretschmer, president-elect, stressed the need of further education of the public regarding medical economics, particularly by general practitioners in their local communities.

Probably the most important action taken by the House of Delegates was the dispatch of a telegram to various authorities in Washington protesting the curtailment of the Specialized Army Training program as it pertains to premedical and medical students. This was considered to be the most serious situation confronting the medical profession today, since it is not possible to fill the enrollment of medical schools with women and physically disqualified men. If enough doctors to offset an approximate annual deficit of 2000 are to be obtained, some way to defer premedical students from the draft must be found.

Much was said about postwar planning. It was recommended that a central bureau be established in Chicago to provide information to physicians returning from service concerning internships, residencies, fellowships, postgraduate courses and so forth. It was stated that the experience gained

in the wartime graduate meetings that have been held so successfully in numerous military hospitals might provide a pattern for future postgraduate teaching.

The House was honored by the presence of Surgeon General Kirk of the Army Medical Corps, and of Surgeon General McIntire of the Navy Medical Corps, both of whom addressed the meeting and were enthusiastically received.

The climax for the Massachusetts delegation came, however, in the privilege of presenting Dr. Roger I. Lee's name for the office of president-elect. The enthusiasm with which the nomination was received and the prompt and unanimous election attest the high regard in which Dr. Lee is held by the House of Delegates. With ten years of service as a trustee, few men have come so well equipped for this exacting and important position. Again, Massachusetts has cause to rejoice.

THE OUTLOOK FOR MENINGOCOCCAL MENINGITIS

Epidemics of meningococcal meningitis are known to occur irregularly in cycles, which usually last from two to five years. There are, in addition, secondary rises and falls in incidence, with peaks occurring during the fall and winter of each year within a large epidemic cycle. During the course of an epidemic a comparison of the incidence of the disease at any time of the year with its occurrence during the corresponding period of the preceding year may therefore give some clue whether the epidemic is waxing or waning, and in this way one may predict whether more or fewer cases are to be expected during the following year and even during the succeeding weeks and months.

A recent summary of the incidence of meningitis, which is included among the morbidity reports of notifiable diseases,[1] indicates that there were more cases during the year 1943 than in 1942. A total of 612,068 cases were reported during the former, and 546,023 cases during the latter. The provisional mortality figures for the first nine months of 1943 show more strikingly the increase in the disease that occurred during that period over the corresponding months of the two previous years.[2] The mortality in thirty-eight states during 1943 was 2.0 per 100,000 of population, as compared with 0.6 during 1942 and 0.5 during 1941. There were deviations from these figures in certain parts of the country, but the great majority of states had rates that were quite similar, both qualitatively and quantitatively. Notable exceptions are Pennsylvania and Montana: in the former the mortalities were respectively two and a half and three and a half times as great in 1941 and 1942 as in 1943, and in the latter the 1943 figure was 8.0 deaths per 100,000 population, as compared with 0.4 for each of the two previous years.

More recent figures, however, offer encouraging evidence that the epidemic is subsiding or at least is beginning to decline. In the morbidity reports for the week ending March 11, 1944,[3] the weekly incidence of meningococcal meningitis was lower than that for the corresponding week last year, this being the first time that a decline had been noted. Subsequent reports[4] showed that the downward trend continued during four successive weeks, but during the week ending April 22, the incidence was slightly higher than in the previous year. Such slight irregularities are to be expected, owing to variations in the occurrence of the disease in different parts of the country, and do not necessarily interfere with the general trend of the epidemic incidence; in fact, the very next report[5] indicates that the downward swing was continuing.

Although the epidemic appears to be subsiding, there will undoubtedly be appreciable numbers of cases of meningococcal meningitis during the coming fall and winter, with a peak that will be appreciably lower than that of the past year. Physicians must still be on the lookout for cases and must treat them early and adequately with sulfonamide drugs to keep the mortality at a minimum. One should also be on the lookout for cases of meningococcemia without meningitis, since such patients respond promptly to sulfonamide therapy and since early treatment usually forestalls meningitis and other focal complications, such as arthritis and endocarditis.

References

1. *Pub. Health Rep.* **59**:376, 1944.
2. *Ibid.* P. 594.
3. *Ibid.* P. 372.
4. *Ibid.* P. 558.
5. *Ibid.* P. 598

MASSACHUSETTS MEDICAL SOCIETY

THE BLUE SHIELD

While countless and voluminous opinions were being expressed concerning legislative proposals for federalized medicine, the sponsors of the Blue Shield sought out the causes for such bills and attempted to neutralize them by more answerable methods.

The Blue Shield in Massachusetts now numbers nearly 35,000 members. Employee groups have been formed in 432 industrial and business organizations. Although more than 3300 Massachusetts doctors have become participating physicians, there are still many members of the profession who have not yet agreed to take an active part in the plan.

Some doctors object to having Blue Shield set a price on their services to the patient. These men should realize, however, that only the low-income subscriber is affected by the set fees, and as time goes on, 100 per cent collections obtainable through Blue Shield will create a better situation than higher fees and 50 to 80 per cent collections. Blue Shield subscribers in the upper-income brackets may be charged by the doctor with the difference between the amount specified in the fee schedule and his regular fee.

A few busy physicians fear that under Blue Shield they would have to serve many more patients than they have time for at present. Such fears are unfounded because Blue Shield guarantees the free choice of patients and in no manner does it insist on doctors taking Blue Shield subscribers as patients whom they would not ordinarily treat.

Several doctors state that they do not agree with the principles of a prepayment plan. This viewpoint is held by an extremely small minority, and is gradually changing to that of the leading physicians in the country, who realize that prepayment is the only answer to a better distribution of medical care. Such doctors may also remember that if the solution to the problem becomes impossible on a voluntary basis, the people themselves, who have already gone on record as desiring an easier method of paying their doctors' bills, will make decisions arbitrarily through legislation.

The Blue Shield is still in its infancy. Its growth has been satisfactory, but if the public demand is to be satisfied, the Blue Shield must receive the same whole-hearted support from physicians that the Blue Cross has obtained from its member hospitals. The latter is now adding members at the rate of a thousand a day.

If you are not yet a Blue Shield participating physician, you are urged to write to the Blue Shield office at 230 Congress Street, Boston 6, for further information.

DEATH

MOODY — Flora F. Moody, M.D., of Springfield, died June 26. She was in her seventy-fourth year.

Dr. Moody received her degree from Tufts College Medical School in 1898. She was a member of the American Medical Association and the Springfield Woman's Medical Club.

Her husband, a son, three sisters and a brother survive.

WAR ACTIVITIES

POSTWAR PLANNING

Bureau of Medical Education Created by New York Academy of Medicine

Anticipating an unprecedented demand for postgraduate medical education on the termination of war, particularly from physicians returning to civil life from service in the armed forces, and from civilian physicians from Central and South America, as well as from European countries released from Nazi control, the New York Academy of Medicine has created the Bureau of Medical Education.

The function of this bureau will be to serve all physicians interested in furthering their medical knowledge, but particularly physicians returning from the war, and the increasing numbers of foreign physicians who come to New York for postgraduate instruction and training. It will be organized by and operated under the supervision of the Committee on Medical Education of the New York Academy of Medicine and will render its services without charge. One of its chief functions will be to publish announcements of postgraduate medical courses conducted by the universities and the hospitals of New York City. Thirty-three of the leading hospitals have been invited to collaborate in this undertaking, and advisers representing the special fields of medical practice have been appointed to supervise the work of the bureau.

MISCELLANY

DEPARTMENT OF MEDICAL SCIENCES ESTABLISHED AT BROWN UNIVERSITY

The establishment of the Department of Medical Sciences at Brown University was recently announced by President Henry M. Wriston. This department will perform a number of important functions within the University and in the relations of the University to the medical profession and hospitals of the community. Charles A. McDonald, M.D., and Alex M. Burgess, M.D., physicians connected with the Division of University Health for some time, have been appointed professors of health and hygiene in this new department.

Dr. Wriston pointed out that through this department the University will assume a larger responsibility for the general education of its students in matters of health as a requisite of effective accomplishment in college and after-college years. He went on to say that special attention will be given to the orientation of students who are planning to enter the medical profession and that the department will offer facilities for advanced study and research, being designed in part to meet the needs and desires of recent graduates of medical schools whose postgraduate studies in certain specialized fields of medical science have been interrupted by war service. Dr. Wriston stated that opportunities for specialized study will also be available to other interested members of the medical profession, emphasizing that the University will be prepared to co-operate in the development of programs of postgraduate study and research for members of the resident staffs of the hospitals of the community.

CORRESPONDENCE

NEW POLICIES OF BOARD OF REGISTRATION IN MEDICINE

To the Editor: On May 17, 1944, the Board of Registration in Medicine voted unanimously that it shall be the policy of the Board, following a hearing, to revoke or suspend, as

the case may be, the registration of any physician who has been sentenced to a penal institution.

On that date the Board also voted unanimously that it shall be the policy of the Board, following a hearing, to revoke or suspend, as the case may be, the registration of any physician who has been committed to and not yet discharged from a mental hospital.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A National Health Service. By Alice Bush, M.D.; J. McMurray Cole, M.D.; E. F. Fowler, M.D.; Elizabeth Hughes, M.D.; Howard Gaudin, M.D.; Selwyn Morris, M.D.; Bruce Mackenzie, M.D.; and Douglas Robb, M.D. 12°, paper, 108 pp. Wellington, New Zealand: Progressive Publishing Society, 1943. 2/6.

In this small pamphlet will be found a description of a plan for the National Health Service in New Zealand. Its practical application is worked out for Auckland City and its suburbs, detail being given in four appendices.

The Nature and Treatment of Mental Disorders. By Dom Thomas V. Moore, O.S.B., Ph.D., professor of psychology and psychiatry, Catholic University of America. With a foreword by Edward A. Strecker, M.D., professor of psychiatry, Graduate and Undergraduate Schools of Medicine, University of Pennsylvania, and consultant and chief of service, Institute of the Pennsylvania Hospital, Pennsylvania. 8°, cloth, 312 pp. New York: Grune and Stratton, 1943. $4.00.

This is a new manual on clinical psychiatry in which emphasis is placed on treatment. The author has appended a classification and definition of clinical entities of psychiatry.

Manual of Fractures: Treatment by external skeletal fixation. By C. M. Shaar, M.D., captain, Medical Corps, United States Navy; and Frank P. Kreuz, Jr., M.D., lieutenant commander, Medical Corps, United States Navy. 8°, cloth, 300 pp., with 148 illustrations. Philadelphia: W. B. Saunders Company, 1943. $3.00.

This manual describes fully the new treatment of external fixation of fractures, which is ideal for use at sea and in mobile hospitals where transportation of patients becomes necessary.

Elements of Medical Mycology. By Jacob H. Swartz, M.D., assistant professor of dermatology, Harvard Medical School and Postgraduate School, and dermatologist, Massachusetts General Hospital. With an introduction by Fred D. Weidman, M.D., professor of dermatological research, University of Pennsylvania. 8°, cloth, 179 pp., with 78 illustrations. New York: Grune and Stratton, 1943. $4.50.

This small manual is designed to serve as a guide to the study of fungus diseases.

The Dysenteric Disorders: The diagnosis and treatment of dysentery, sprue, colitis and other diarrhoeas in general practice. By Sir Philip Manson-Bahr, C.M.G., D.S.O., M.D., F.R.C.P., senior physician to the Hospital for Tropical Diseases and the Royal Albert Dock and Tilbury hospitals, consulting physician in tropical diseases to the Dreadnought Seamen's Hospital, London, director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, consulting physician to the Colonial Office and Crown Agents to the Colonies, consultant in tropical medicine to the Admiralty and to the Royal Air Force, and Lumleian Lecturer, Royal College of Physicians, 1941. With an appendix by W. John Muggleton, M.S.M., F.I.M.L.T., technical assistant. Second edition. 8°, cloth, 629 pp., with 23 plates and 108 illustrations. Baltimore: The Williams and Wilkins Company, 1943. $10.00.

The first edition of this book was printed in 1939, and the second edition has been called for by the necessity of including many advances in etiology, diagnosis and treatment that have become available since its first publication. No drastic alterations have been made in the arrangement of the book, but much new knowledge has been incorporated in its proper place throughout the various chapters. A new chapter on pellagra has been inserted, emphasizing the etiology of the sprue syndrome and its relation to the steatorrheas. Discussion of the treatment of bacillary dysentery with sulfaguanidine has been included.

NOTICES

MEDICOLEGAL CONFERENCE AND SEMINAR

The Massachusetts Medico-Legal Society in conjunction with the medicolegal departments of Harvard, Boston University and Tufts medical schools has arranged for an all-day conference to be held at the Mallory Institute of Pathology, Boston City Hospital, on Wednesday, October 4, 1944. It will include lectures, demonstrations, and informal discussions concerning many subjects in legal medicine, particularly stressing some of the more recent procedures. This meeting will be open to any registered physician, lawyer, police official, senior medical student or other medical investigator who may be interested and care to register. No limit in number has been made. There will be no fee for registration. Although advance application is not essential, it would be helpful to those arranging the conference if notice of intention to attend be sent prior to October 1 to Dr. W. H. Watters, Department of Legal Medicine, Harvard Medical School, Boston 15.

The Harvard Medical School, Courses for Graduates, with the co-operation of the medical schools of Boston University and Tufts College, offers a seminar in legal medicine to occupy the entire week of October 2 to 7, inclusive. It is planned particularly for medical examiners and coroners physicians but will be open to any other suitable graduate of an approved medical school. The course will be practical rather than theoretical and will consist of autopsy demonstrations, technic and interpretation of laboratory tests, study of the day-by-day cases of a medical examiner, round-table conferences, and the many subjects now included in the widening field of legal medicine. In order that each participant may receive the maximum benefit, the enrollment has been limited to fifteen. For the seminar the fee is $25. Application should be made on or before October 1 to Harvard Medical School, Courses for Graduates, 25 Shattuck Street, Boston 15.

NEW YORK INSTITUTE OF CLINICAL ORAL PATHOLOGY

The New York Institute of Clinical Oral Pathology announces its first open meeting, to be held at the New York Academy of Medicine on Monday evening, October 30, in Hosack Hall. Outstanding investigators will participate in a symposium "Fluorine and Dental Caries."

Members of the medical, dental, public-health and other professional groups are cordially invited. For further information all communications should be addressed to G. Roistacher, Executive Secretary, 101 East 79th Street, New York 21, New York.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, July 27

Monday, July 31

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, August 1

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

(*Continued on page xiii*)